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The American Journal of Medicine

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Clinical Studies

Studies on Chronic Thyrotoxic Myopathy . GEORGE W. THORN AND HOWARD A. EDER 583

Disabling myopathies may be the presenting feature in thyrotoxicosis. The authors discuss fully and instructively the various types of thyrotoxic myopathy, the occasional difficulties in diagnosis and the gratifying results of treatment of the underlying thyroid disease. Five illustrative cases of chronic thyrotoxic myopathy and two combining myasthenia gravis with thyrotoxicosis are presented in detail. Possible mechanisms are considered, with special reference to inadequate synthesis of creatine phosphate.

Disturbance in Salt and Water Metabolism in Hypertension
GEORGE A. PERERA AND DAVID W. BLOOD 602

Rigid withdrawal of sodium chloride from the diet resulted in significant weight loss and increased urinary output in non-hypertensive subjects but not in patients with hypertensive vascular disease. This difference in response indicates a disturbance in salt and water metabolism in hypertension, referable to renal changes probably mediated by the adrenal cortex.

Thiouracil in Angina Pectoris WILLIAM S. REVENO 607

An interesting study of the effects of thiouracil and propyl-thiouracil in eight patients with angina pectoris. Six of the patients improved as a result of "chemical thyroidectomy."

Effects of Quinacrine (Atabrine) Suppression on the Course of Pacific Vivax Malaria
CAPT. IRVING M. LONDON, CAPT. PAUL H. LAVIETES, CAPT. KENNETH E.
PETERSON AND MAJOR HARRY MOST 615

The incidence of relapse in vivax malaria after termination of suppressive therapy with quinacrine was 82 per cent, about the same relapse rate as was observed in a 120-day period following treatment without suppression. The authors question the advisability of prolonged routine suppression in non-endemic areas.

"Muscle Spasm" in Acute Low Back Pain and Similar Syndromes. A New Method of
Treatment with Curare (d-Tubocurarine in Oil and Wax)
EDWARD B. SCHLESINGER AND CHARLES RAGAN 621

The authors describe striking results obtained by treatment of "muscle spasm," particularly in "low back" and similar syndromes, with *d*-tubocurarine in oil and wax. The myoneural block effected by curare makes it possible to break the vicious cycle of splinting and pain.

Subacute Bacterial (Streptococcus Viridans) Endocarditis Treated with Penicillin
ROBERT L. McMILLAN 628

Subacute bacterial endocarditis and its treatment with penicillin are considered, with an account of twelve cases, eleven of which are alive and well twelve to twenty-four months after therapy.

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- Folic Acid and the Bone Marrow in Radiation Therapy . . . PERK LEE DAVIS 634
Folic acid, given as adjunct in the treatment of sixty-nine patients with lymphoblastoma receiving prolonged radiation therapy, seemed to decrease the depressant effects of radiation on the bone marrow.

- Clinical Vibrometer. An Apparatus to Measure Vibratory Sense Quantitatively
WILLIAM S. COLLENS, JAMES D. ZILINSKY AND LOUIS C. BOAS 636
The authors describe a new instrument for quantitatively measuring impairment in vibration sense, intended particularly for use in the detection of peripheral neuritis.

- Impaired Vibratory Sense in Diabetes
WILLIAM S. COLLENS, JAMES D. ZILINSKY AND LOUIS C. BOAS 638
Applying the clinical vibrometer to a study of vibratory sense in diabetics, the authors found an unexpectedly high incidence of peripheral neuropathies without overt clinical manifestations.

- Planning of a Camp for Diabetic Children HENRY J. JOHN 642
Dr. John here gives practical advice concerning the planning and operation of a summer camp for diabetic children, based on his long experience as director of such a camp. The problems involved have both medical and social significance.

Reviews

- Differential Diagnosis in Obscure Fever MICHAEL J. HORAN, JR. 649
An interesting review of the mechanisms of fever production, the various causes of fever and useful approaches to the differential diagnosis of fever of obscure origin.

- Treatment of Severe Functional Headaches
JOSEPH W. GOLDZIEHER AND MAX A. GOLDZIEHER 656
A general summary of recent developments in the causes and treatment of migraine and other severe types of headache.

Seminar on the Therapeutic Use of Antibiotics

- Penicillin in the Treatment of Syphilis FRANK W. REYNOLDS 661
A critical appraisal of the current status of penicillin, given alone or concurrently with other therapy in the treatment of early syphilis, neurosyphilis, benign late syphilis, cardiovascular syphilis, latent syphilis, early congenital syphilis and syphilis in pregnant women. Recommended dosages and schedules for treatment are given.

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Clinico-pathological Conference

- Chronic Granuloma 694
 Clinico-pathological Conference (Washington University School of Medicine)—A problem in the differential diagnosis of chronic granulomas and lymphomas. The discussion is instructive and interesting. The diagnosis remained in doubt until histological study of the sections was completed.

Case Reports

- Extensive Polycystic Disease of the Kidneys and Liver . . . AARON M. LEFKOVITS 704
 An interesting example of polycystic disease.
- Mycotic Lung Infection ROGER A. HEMPHILL 708
 An instance of aspergillus infection involving a lung cyst.

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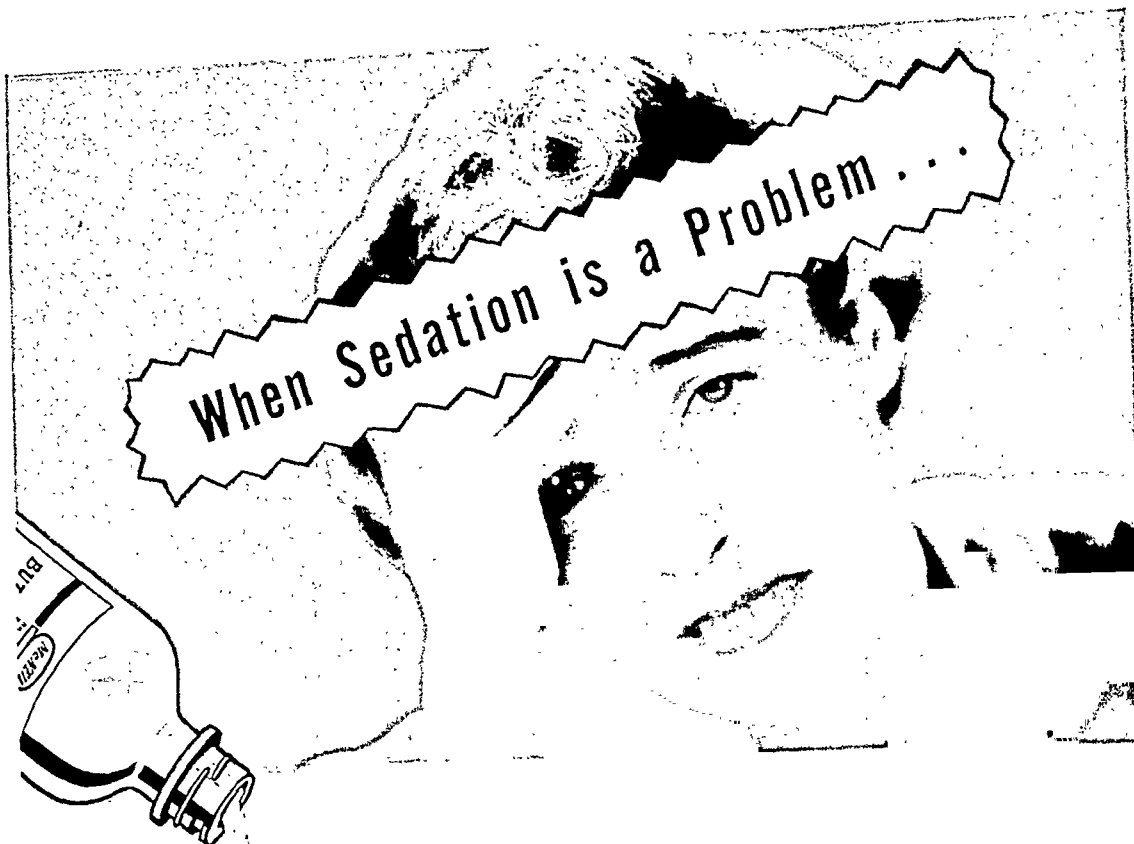
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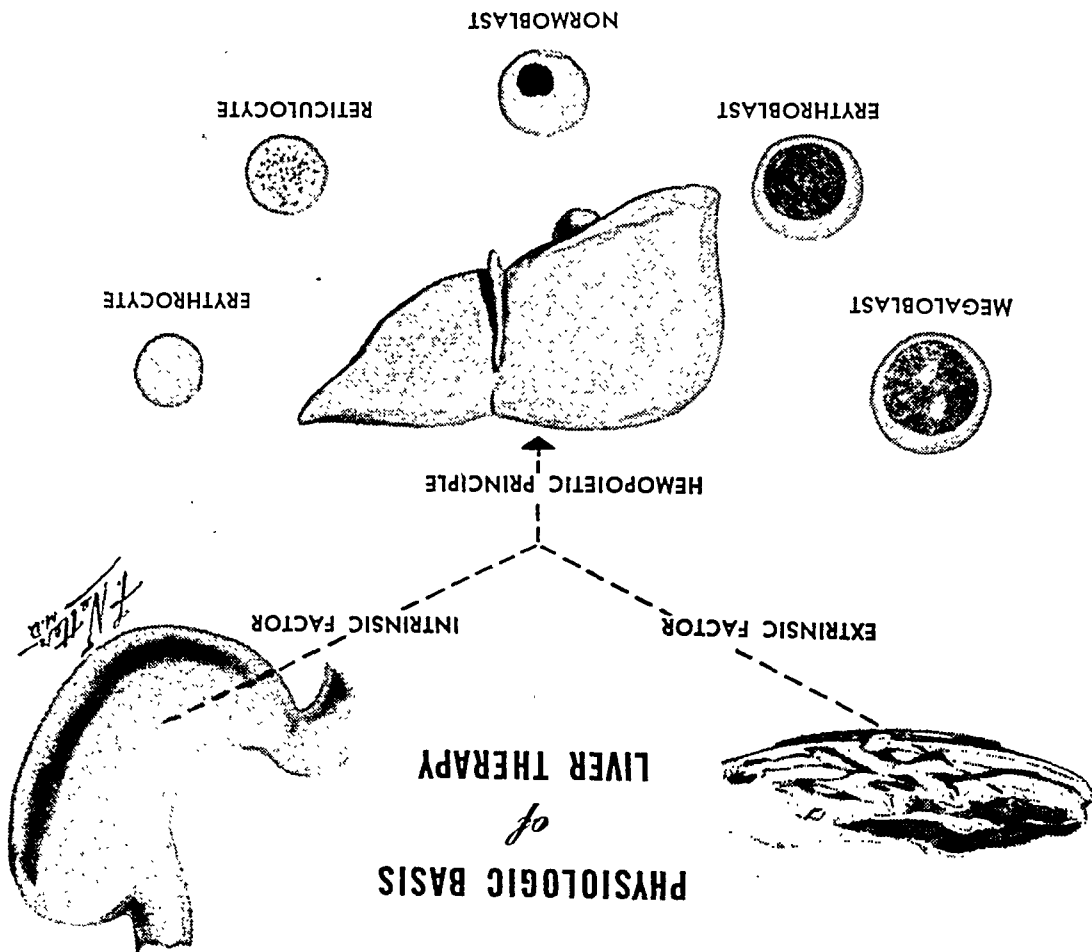
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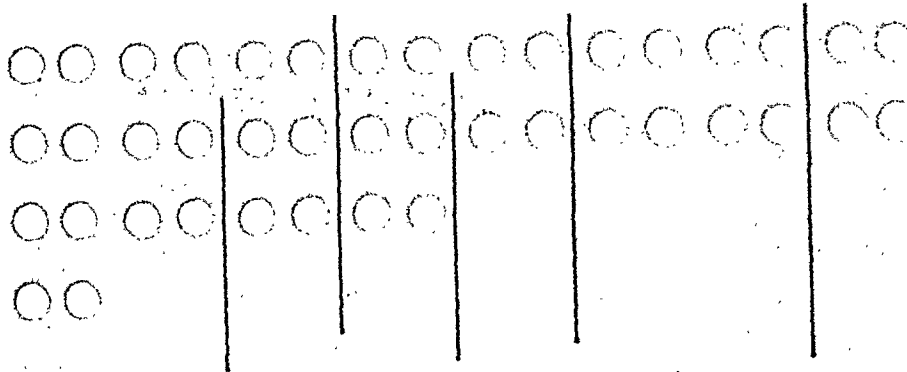
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Studies on Chronic Thyrotoxic Myopathy*

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BOSTON, MASSACHUSETTS

MUSCULAR weakness is a common accompaniment of thyrotoxicosis, and it is well known that many patients with severe thyrotoxicosis manifest striking impairment in muscular function.¹ There are, in addition, patients with thyrotoxicosis in whom the signs and symptoms of muscular weakness may be entirely out of proportion to the degree of thyrotoxicosis. In some of these patients the usual clinical signs of thyrotoxicosis may be so slight or obscure as to be overlooked. These instances, although not common, merit consideration because of the striking improvement in muscular strength and development which may follow treatment of the underlying thyrotoxicosis.

Starling, Darke, Hunt and Brain² have suggested the following classification of myopathies associated with thyrotoxicosis: (1) Exophthalmic ophthalmoplegia; (2) thyrotoxic myopathy, (A) acute thyrotoxic myopathy, (B) chronic thyrotoxic myopathy, (C) thyrotoxic periodic paralysis; and (3) myasthenia gravis and thyrotoxicosis.

Exophthalmic ophthalmoplegia^{2,3} is a disorder localized in the soft tissues and muscles of the orbits. It frequently persists after thyroidectomy and in some instances actually progresses postoperatively. Recent studies by Rundle and Pochin⁴ suggest that the exophthalmos is due to an increased fat content of the retrobulbar tissues. Severe generalized muscular disease has rarely been noted in patients with this condition.²

Acute thyrotoxic myopathy as described by Heuer⁵ in 1916 appears to be a rapidly progressive myasthenia with involvement of the bulbar muscles as well as of the muscles of the limbs and trunk. It is usually fatal in one to two weeks, and death occurs most frequently from respiratory paralysis. In the case described by Heuer the differentiation from myasthenia gravis was made largely on the basis of response to faradic stimulation. It is questionable whether these cases represent a distinct entity rather than thyrotoxicosis associated with myasthenia gravis.

Thyrotoxic periodic paralysis not uncommonly occurs in conjunction with familial periodic paralysis. This condition should be distinguished from chronic thyrotoxic myopathy by the fact that patients are asymptomatic between attacks and their muscles appear to be normal. To date, thirty-five such cases have been described (Talbot⁶). In some instances thyroidectomy may cause a complete remission of symptoms (Dunlop and Kepler⁷), while in others there was merely a decrease in the frequency of attacks (Morrison and Levy⁸). The association of changes in serum potassium concentration with attacks of periodic paralysis is well known.⁹ The mechanism whereby excessive thyroid hormone affects the disease is not understood.

Chronic thyrotoxic myopathy is one of the most important muscular disturbances associated with hyperthyroidism. It is char-

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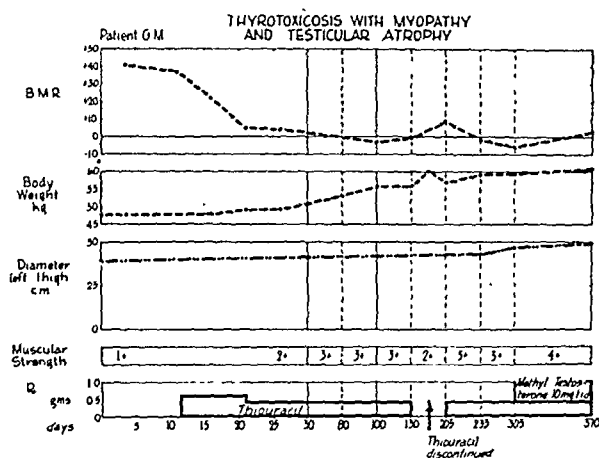


CHART 1.

acterized by marked muscular atrophy which is symmetrical and most frequently involves the shoulder and pelvic girdles. It was first described in 1895 by Bathhurst.¹⁰ The literature has recently been summarized by McEachern and Ross¹¹ who have reported thirteen such cases including three of their own.

We wish to report five additional cases of this disease which were seen over a relatively short period at the Peter Bent Brigham Hospital and to emphasize the importance of recognizing these cases because of the dramatic improvement which may follow correction of the underlying thyrotoxicosis.

CASE REPORTS AND OBSERVATIONS

The principal features in the five cases of chronic thyrotoxic myopathy are summarized in Table 1.

CASE 1. A fifty-year old male presented generalized muscular weakness with striking atrophy of the muscles of the shoulder girdle. Signs of thyrotoxicosis were minimal; gonadal atrophy was present. The patient made an excellent response to thiouracil therapy supplemented later with methyl testosterone. (Chart 1.)

G. M., No. M65090, a fifty-year-old Italian mill worker, entered the Peter Bent Brigham Hospital on October 6, 1943, because of marked weakness. For thirty years the patient had tolerated warm weather poorly. He had always been comfortable in cold weather and frequently slept only with a sheet, even in cold weather. During the seven months before admission these

symptoms became more pronounced, and, in addition, he had noted marked muscular weakness, especially of his legs. For eight weeks this had been so pronounced that he had been unable to climb stairs and spent most of his time in bed. During this period he had noted rapid heart action, and ankle edema had occurred at the end of the day. He had lost approximately 30 pounds, and his appetite had not been as good as usual.

The patient's family history was non-contributory, and his past history was not noteworthy except for a marked decrease in potency.

Physical examination on admission showed a middle-aged, dark Italian lying quietly in bed with a slight amount of restlessness. His temperature was 98°F., pulse 104, respirations 16 and blood pressure 140/70 mm. Hg. His skin was warm but not moist except in the palms. There was marked muscular atrophy, especially in the muscles of the shoulder girdle with marked winging of the scapulae and marked atrophy of the supraspinatus and biceps muscles. There was also atrophy of the legs, especially of the quadriceps. Muscles of the forearms and lower legs did not show such marked atrophy. There was no fasciculation. His gait was unsteady; he walked with a broad base and was unable to climb stairs at all. He did not have exophthalmos or other eye signs. There was a definite fine tremor to the tongue and outstretched hands. The thyroid was enlarged but contained no nodules, and a bruit could be heard over it. The lungs were normal. The heart was not enlarged, the sounds were forceful, and there was a grade 1 systolic murmur at the apex. The abdomen was normal. The genitalia were small with small testes, and the prostate was also small. There was slight pitting edema of the ankles. Neurological examination showed nothing abnormal except the muscular weakness. Reflexes were physiological.

Laboratory examination revealed the following: Blood serology was negative. Urine specific gravity was 1.015 with no protein or sugar. Sediment contained many white cells. Hemoglobin was 12.2 Gm. per cent, hematocrit 35 per cent, and sedimentation rate 22 mm. per hour (method of Wintrobe). The white blood count was 8,250, and smear appeared normal.

TABLE I
THYROTOXIC MYOPATHY

Patient.	G. M. Case I	M. S. Case II	E. M. Case III	J. B. Case IV	Y. C. Case V
Sex and age.	Male, 50 years	Male, 40 years	Female, 43 years	Female, 56 years	Female, 22 years
Duration of symptoms.	7 months	2 months	6 months	6 months	6 months
Thyroid enlargement.	+	+	++	0	++
Eye signs.	None	Lid lag	Stare, lid lag	None	Exophthalmos, stare, lid lag, impaired convergence
Tremor.	+	+	++	0	+
Muscular involvement	Generalized weakness and atrophy, most marked in shoulder girdle	Generalized weakness with atrophy especially in arms	Generalized weakness and atrophy; regurgitation of fluids	Extreme generalized weakness and atrophy	Generalized weakness; atrophy especially in upper arm
Fasciculation.	0	0	0	0	0
Initial basal metabolic rate—%..	+37	+40	+60	None taken	+33
Spontaneous creatinuria mg./24 hours.	100	200	590	Not done	420
Creatine tolerance test*					
% retention of ingested creatine.	62	28	Not done	Not done	Not done
Urinary 17-ketosteroids mg./24 hours.	8.3	8.6	2.7	Not done	9.4
Cardiac enlargement by x-ray—%.....	0	0	+25	0	+10
Circulation time—seconds**.....	9	Not done	11	Not done	14
Prostigmine test..	No improvement	No improvement	No improvement	Not done	No improvement
Treatment.	Thiouracil for 1 year; methyl testosterone for 2 months	Subtotal thyroidectomy; methyl testosterone; testosterone propionate for 4 months	Thiouracil for 9 months; thyroidectomy	Iodine for 2 days	Thiobarbital for 5 months
Result.	Strength returned almost to normal	Strength returned to normal until onset of hypothyroidism	Strength returned almost to normal	Died	Good return of strength
Basal metabolic rate after treatment.	—3% (18 months)	—22% (6 months)	+20% (18 days)	—3% (5 months)

* Normal for males 85–100% retention; normal for females 80–95% retention.
 ** Decholin, arm to tongue; normal 15–18 seconds.

Blood urea nitrogen was 11 mg. per cent, non-protein nitrogen 37 mg. per cent, total protein 6.2 Gm. per cent, albumin 4.0 Gm. per cent, globulin 2.2 Gm. per cent, fasting blood sugar 99 mg. per cent, blood cholesterol 175 mg. per cent, calcium 5.6 m.M. per liter, phosphorus

1.56 m.M. per liter, and alkaline phosphatase 3.7 Bodansky units. Stool examination was normal. Arm to tongue circulation time (decholin) was 9 seconds. Prostigmine test showed no increase in muscular strength after administration of 1.5 mg. of prostigmine subcutaneously.

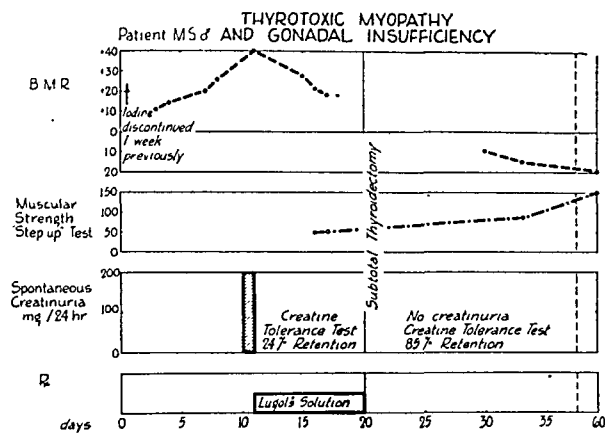


CHART 2.

Sulkowitch test for calcinuria was 4+. He excreted 0.100 Gm. of creatine per twenty-four hours. Creatine tolerance test showed retention of only 62 per cent of ingested creatine (normal 85 to 100 per cent retention). The hippuric acid test showed 1.17 Gm. excretion in one hour. Urinary 17-ketosteroid output was 8.3 mg. per twenty-four hours. The electrocardiogram was normal. X-ray films of the heart showed no apparent enlargement; the lungs were clear and there was no substernal thyroid. The basal metabolic rate before treatment ranged from +50 to +37 per cent.

The patient's metabolic rate dropped from +50 to +37 per cent on bed rest. (Chart 1.) On the tenth hospital day he was started on 0.6 Gm. of thiouracil daily. This was maintained until discharge, thirty-three days later. His basal metabolic rate fell steadily and after eleven days of treatment was +5 per cent. He showed no marked improvement in muscular strength, however, until shortly before discharge when he was able to walk up stairs without holding onto the rail. Strength of his hands tested with a dynamometer showed no appreciable increase. Symptomatically he felt much better. He no longer complained of sweating. His appetite was improving, and he gained 1.2 kg. in the hospital. The creatine tolerance test at time of discharge showed that he retained 96 per cent of the ingested creatine. He was followed in the metabolic clinic where his basal metabolic rate ranged from +4 to -3 per cent. His weight steadily rose so that on February 15th he weighed 59 kg. and his weight remained at this level. The change in appearance of his muscles at this time was striking. There was no

longer any evidence of muscular atrophy, and he was able to climb stairs with ease. On March 28th he complained of swelling of his face and arms (myxedema), and thiouracil was discontinued for a month. It was then resumed. His basal metabolic rate ranged from -2 to +6 per cent, and his weight remained constant. He still felt that he did not have complete return of muscle strength. Although he had returned to work, he could not do as heavy work as he could before this illness.

He was readmitted to this hospital on August 8, 1944, for re-examination. Physical examination showed striking increase in the size of his muscles, and this was corroborated by measurements. The thyroid was no longer palpable; the heart was not overactive, and the testes were atrophic as previously described. Basal metabolic rate was -5 per cent. He excreted 0.74 Gm. of creatinine and 0.23 Gm. of creatine per twenty-four hours. The Wilder test was negative. His urinary 17-ketosteroid excretion was 10.1 mg. per twenty-four hours. He was able to do 5166 foot-pounds of work using the step test. He was discharged on 30 mg. of methyl testosterone daily.

On this medication he felt definite increase in strength, almost to complete restoration of normal. His potency increased so that he was able to have satisfactory intercourse. After one month he stopped testosterone. During the following month his strength continued to improve until he felt as strong as before his illness. His potency, however, diminished. Physical examination on October 17, 1944, showed increase in weight of 2 kg. and increase in size of his muscles. There was no further increase in muscle strength by the step-up test.

CASE II. A forty-six-year-old male complaining of generalized muscular weakness, involving particularly the right arm, showed atrophy of both arms. The patient also had testicular atrophy. Signs of thyrotoxicosis were minimal. The patient's muscular strength responded strikingly to iodine therapy followed by subtotal thyroidectomy and subsequently supplemental testosterone therapy. (Chart 2.)

M. S., No. M64175, a forty-six-year-old salesman, entered the Peter Bent Brigham Hospital on May 11, 1943, because of marked muscular

weakness for two months. He had been in good health until six months prior to admission when he noted a choking sensation on swallowing with a sense of fullness in his epigastrium. On a regimen of atropine and aluminum hydroxide, these symptoms had subsided. Two months before admission he had begun to feel tired and noted weakness of his muscles with difficulty in walking. In the week prior to admission the slightest exertion had caused him to break out in a cold sweat with a generalized aching in his bones and muscles. During the previous month he had lost 18 pounds despite the fact that his appetite had been as good or better than before. In addition, he had noted some palpitation, nervousness, a tendency to sweat easily and a slight tremor of his hands. He had been placed on Lugol's solution by his local physician and had continued this up to four days prior to admission. The remainder of the patient's past history and his family history were non-contributory.

Physical examination on admission showed a well nourished, white male who was very restless and nervous. His temperature was 99°F., pulse 90, respirations 20 and blood pressure 130/80 mm. Hg. His weight was 64 kg. He showed generalized muscular weakness of a mild degree, somewhat greater in his right arm than in his left, with some loss of muscle substance on the right. His reflexes were normal. The skin was warm and of fine texture, and he was sweating freely. His hair was normal in distribution and appearance. The eyes were not unusually prominent, but there was slight lid lag. There was a fine tremor of the tongue. Thyroid was slightly enlarged with a slight bruit over the right lobe. The lungs were clear, the heart was not enlarged, and sounds were not hyperactive. There was a grade I systolic murmur at the apex. The abdomen was not remarkable and there was no significant tremor of the hands. His testes were small, and his prostate was soft.

Laboratory examination revealed the following: Blood serology was negative. Urine specific gravity was 1.012, no protein or sugar. Sediment was negative. Hemoglobin was 13.5 Gm. per cent, hematocrit 42 per cent, sedimentation rate 6 mm. per hour. White blood count was 9,000 with 58 per cent neutrophils and 38 per cent lymphocytes. The red cells appeared normal.

Blood urea nitrogen was 10 mg. per cent. Total protein was 6.3 Gm. per cent, albumin 3.2 Gm. per cent, globulin 3.1 Gm. per cent. Fasting blood sugar was 115 mg. per cent, carbon dioxide combining power 25.8 m.M. per liter, serum chloride 97 m.Eq. per liter, cholesterol 149 mg. per cent, urine 17-ketosteroids 8.6 mg. per twenty-four hours. The stool was normal. While on a creatine-free diet he excreted 0.201 Gm. of creatine in twenty-four hours. He retained only 28 per cent of the ingested creatine (2.6 Gm.) in the creatine tolerance test. The electrocardiogram showed normal curves and the chest film was normal. The gastrointestinal series was normal except for pylorospasm, and the barium enema was also normal. After 1.5 mg. of prostigmine subcutaneously, he showed no increase in muscular strength. His initial basal metabolic rate was +11 per cent.

During his hospital stay he ran a low-grade fever while on bed rest. (Chart 2.) His basal metabolic rate gradually rose from +11 to +40 per cent on his eleventh hospital day. (He had been on Lugol's solution before admission.) He was then placed on Lugol's solution and in six days his basal metabolic rate fell to +19 per cent, his creatine excretion dropped to 0.015 Gm. per twenty-four hours, and subtotal thyroidectomy was performed. The gland showed hyperplasia with iodine involution. After operation his basal metabolic rate continued to drop and was -14 per cent on June 10th, at the time of discharge from the hospital. After operation he had no spontaneous creatinuria, and he retained 84.4 per cent of the ingested creatine in the tolerance test. His strength rapidly increased. Before operation he could step up and down on the 12-inch step for only 50 seconds; after operation he was able to go for 88 seconds. One month after operation he was able to do this work for 150 seconds. After returning home his strength improved. He gained 10 kg. and was able to return to work. He continued in good health until October, 1943, when he began to feel fatigued and began to note slowness of action and thought. His basal metabolic rate fell to -20 per cent, and he was readmitted in November, 1943, with signs and symptoms of myxedema. His cholesterol at that time was 500 mg. per cent.

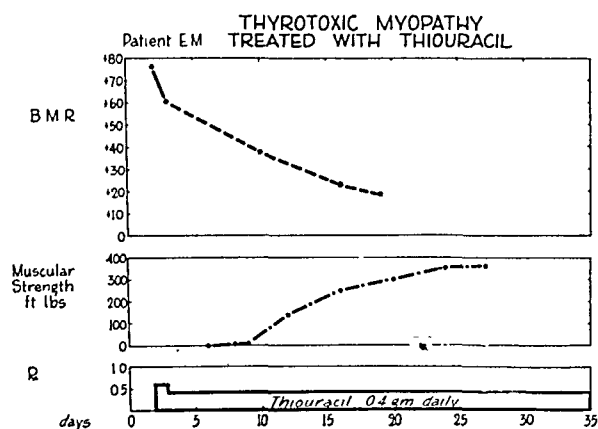


CHART 3.

Creatine tolerance test showed retention of 84 per cent of the ingested creatine. He was somewhat weaker and was able to raise himself on the 12-inch step for 90 seconds. He was started on 60 mg. of thyroid daily and has since lost his signs of myxedema.

After discharge he still complained of some muscular weakness although there was no evidence of atrophy. Since it had been noted that his testes were small, prostate soft, and libido was absent, he was started on 30 mg. of methyl testosterone daily. After one month he showed appreciable improvement and was able to work ten hours a day. The following month he received testosterone propionate 25 mg. daily for three days and bi-weekly thereafter. On this medication his strength returned completely to normal, and he was able to work on the step for 115 seconds.

CASE III. This was a forty-three-year-old female with extreme muscular weakness and generalized muscular atrophy. Signs of thyrotoxicosis were clearly evident. Treatment with thiouracil resulted in a prompt and striking improvement in muscular strength as well as in size of muscles. (Chart 3.)

E. M., No. M65818, a forty-three-year-old housewife, entered the Peter Bent Brigham Hospital on February 3, 1944, because of such extreme weakness that she had been unable to get out of bed for the previous three weeks. She had felt quite well until six months before admission when she had noted marked weakness of her arms and legs with fatigue after very slight exertion. This weakness had become progressively worse, and for several months she had been unable to climb stairs. For three

weeks she had been too weak to get out of bed, and she said that exertion made the weakness more marked. For several months her speech had been thick. There had been occasional regurgitation of fluids into her nose, but she had had no diplopia. She had always been uncomfortable in hot weather. Since her present illness, her appetite had been poor and she had lost 30 pounds. In addition, she had become nervous and irritable and had noted palpitation. Her local physician had told her that her heart was irregular but that she had no symptoms of heart failure. Four months previously she had noted swelling of her neck but had had no hoarseness or difficulty in swallowing. Her physician had prescribed iodine which had been followed by marked relief of symptoms, but this therapy had not been continued. The remainder of the patient's past history was non-contributory.

The family history was of interest in that she had one sister with a goiter of three years' duration.

Physical examination on admission showed an extremely thin woman with evidence of marked weight loss. Her temperature was 98.6°F., pulse 106, respirations 32, blood pressure 130/64 mm. Hg. She was very weak and could not sit up unsupported. The skin of her face had a pinkish hue; her palms were warm and moist; and there was marked wasting of all muscles. Her eyes were prominent with a definite stare and lid lag. Retinal vessels were normal. She had a marked tremor of the tongue. The thyroid was visibly enlarged in both lobes, and there was a definite bruit. It was not nodular. She had definite tremor of the outstretched hands. Her lungs were normal; her heart was slightly enlarged; the sounds were forceful. There was a grade 1 systolic bruit at the apex and base. The liver could be felt below the costal margin. She had no enlargement of the spleen or kidneys. Her reflexes were normal. She had marked hypotonia of her muscles. Her speech was thick, but it did not become worse on continuous effort.

Laboratory data revealed her blood serology to be normal. Urine specific gravity was 1.024 with no protein or sugar; sediment was clear. Hemoglobin was 12 Gm. per cent, hematocrit

43 per cent, sedimentation rate 7 mm. per hour. White blood count was 7,700 with 71 per cent neutrophils. The smear appeared normal. Blood urea nitrogen was 9 mg. per cent. Total protein was 5.4 Gm. per cent, albumin 2.7 Gm. per cent, globulin 2.7 Gm. per cent. Non-protein nitrogen was 29 mg. per cent. Fasting blood sugar was 96 mg. per cent. Serum cholesterol ranged between 128 and 242 mg. per cent. She excreted 0.59 Gm. of creatine in twenty-four hours. A throat culture showed *Streptococcus* (alpha) and *Staphylococcus aureus*. Circulation time was 11 seconds on admission (arm to tongue decholin). The chest film showed the heart to be 25 per cent above average. The lungs were clear, and there was no substernal thyroid. Bone films showed normal detail with no osteoporosis. An electrocardiogram showed auricular fibrillation with inverted T₄. Repeated electrocardiogram showed normal sinus rhythm with left axis deviation. Initial basal metabolic rates were +76 per cent and +60 per cent.

The patient was started on thiouracil 0.4 Gm. daily. (Chart 3.) On her fifth day of treatment her basal metabolic rate was +38 per cent. At that time she had her second attack of paroxysmal auricular fibrillation, the first being on the day of admission. She had normal sinus rhythm with sinus tachycardia at all other times. During her hospital stay her basal metabolic rate fell steadily until it was +20 per cent at the time of discharge. Her pulse rate decreased also and was 80 at the time of discharge, whereas it had been 110 on admission. Her circulation time (decholin) increased to 15 seconds.

The most striking changes, however, were in her strength. She was able to walk around, whereas on admission she could not even sit up in bed. Her muscle strength as tested by standard work showed a 64-fold increase. She was alert and wide awake. Her skin was less warm but she still had slight tremors. Her appetite improved markedly, although there was no weight gain. Her heart was regular; sounds were not especially forceful. The systolic murmur at the apex disappeared. The thyroid was slightly larger and more firm. The bruit was still present but was markedly diminished. She was discharged on her thirty-first hospital day to continue on thiouracil medication. When last

heard from after two and one-half months she had gained 9 kg. and was up and around and able to do most of her housework.

CASE IV. A fifty-six-year-old female with extreme weakness and generalized muscular atrophy, had practically no signs of thyrotoxicosis. Her progress in the hospital was rapidly downhill with death on the seventh hospital day. Pathological examination revealed hyperplasia of the thyroid, striking atrophy of the skeletal muscles and of the *glomerulosa layer* of the *adrenal cortex*.

J. B., No. M64553, a fifty-six-year-old colored housewife, was admitted to the Peter Bent Brigham Hospital on July 9, 1943, because of palpitation and progressive fatigability of three months' duration. For six months previous to admission it had been noted that the patient desired cool surroundings and preferred cold to hot weather. At that time she also had complained of generalized weakness. Later this had become so pronounced that even climbing a short flight of stairs had produced severe fatigue, compelling her to rest in a chair from five to fifteen minutes thereafter. Two months later, because of steadily increasing weakness, she had been forced to cease work as a dressmaker. At the same time she had noticed palpitation. She had been seen by her family physician who found a tachycardia of 110–128, and she had been slowly digitalized. Palpitation had persisted up to the time of admission. The weakness had gradually increased, and one week before admission it had become so severe that she had had to stay in bed all the time. Two days before admission, she had been so weak that she needed constant nursing attendance. She became dyspneic on the slightest exertion. Just prior to admission, it had been noted that her speech was thick and that she had difficulty in pronouncing her words. The patient had lost weight during this illness, but the exact amount was not known.

Her past history included an episode five years before admission of swelling, redness and tenderness of her left ankle and knee. A diagnosis of acute rheumatic fever had been made at that time. The family history was non-contributory.

Physical examination on admission revealed a drowsy colored woman showing evidence of marked weight loss. Her temperature was 100.6°F., pulse 108, respirations 22 and blood pressure 140/80 mm. Hg. She appeared lethargic and spoke in a slow lisping voice. In the middle of the interview she became dyspneic and exhausted and lapsed into sleep. Her skin was warm and dry. There was partial alopecia at the temples and frontal regions. There was no evidence of oculomotor weakness. The pupils were equal and reacted to light and accommodation. There was no exophthalmos or abnormal eye signs and the ocular fundi were normal. The tongue was coated, was not atrophic and was without fibrillary twitchings. Neck veins were not distended. The thyroid was small and palpable without an audible bruit. The lungs were emphysematous but without râles. The heart was not enlarged, and the rhythm was regular with many extrasystoles. There was a systolic murmur heard over the entire precordium, loudest at the base. The abdomen was normal. Extremities showed generalized muscle wasting, most marked in the forearms, hands, calves and feet. There were no fasciculations. There was marked muscular weakness. The patient was unable to hold her hands out in front of her for more than half a minute and was barely able to lift more than one leg off the bed at a time. The only reflexes obtained were hypoactive biceps and knee jerks.

Laboratory examination revealed the following: Urine was not remarkable except for a trace of protein. Blood serology was normal. Red blood count 5.0 million. Hemoglobin was 14.5 to 16.0 Gm. per cent, hematocrit 45 per cent, sedimentation rate 17 mm. per hour, white blood count 6,000 to 10,000 with 58 per cent neutrophils. Platelets were present in normal amounts; the smear appeared normal. Blood urea nitrogen was 13 mg. per cent and non-protein nitrogen was 20 mg. per cent. Total protein was 8.6 Gm. per cent with 3.4 Gm. per cent albumin. Fasting blood sugar was 117 mg. per cent, carbon dioxide combining power 30.8 m.M. per liter, serum chloride 100 m.Eq. per liter. Spinal fluid was clear and colorless. No cells were present, and the dynamics were normal. Hinton and gold sol were

negative. Electrocardiogram showed a sinus tachycardia with a ventricular rate of 120. There were premature auricular beats, left axis deviation, inverted T_1 and T_4 and a slightly elevated ST_4 .

The patient ran a rapidly downhill course with a gradual rise of temperature, pulse and respiration rate. On the second day she was much more drowsy and the weakness was much more striking than on admission. She spoke with a thick voice and enunciation was poor. At no time, however, was there facial or hypoglossal paralysis. A chest film showed the heart to be normal in size and shape with some blunting of the left costophrenic angle. The heart beat was rapid and of small amplitude. On the fifth hospital day her temperature rose to 104.3°F., pulse to 100, respirations to 40. From this point on she was continuously stuporous, incontinent and required parenteral fluid administration. On the fifth day she also received 10 drops of Lugol's solution. The following day she received 1 Gm. of sodium iodide, 5 Gm. of sodium sulfadiazine, and 3 cat units of digitalis intravenously. This did not alter her course. Her temperature rose to 107.2, with a pulse of 168, and she died on her seventh hospital day.

Postmortem examination showed the thymus to be enlarged; it weighed 26 Gm. The heart weighed 340 Gm. and appeared normal. The abdominal viscera appeared normal except for a small argentaffinoma in the cecum, healed salpingo-oophoritis and a small leiomyoma of the uterus. The liver weighed 1,100 Gm. The kidneys were normal. The adrenals grossly were not remarkable. The thyroid weighed 40 Gm. and seemed to be slightly enlarged and nodular.

Microscopic examination showed moderate congestion of the sinusoids and central veins of the liver. The adrenal cortex (Fig. 1) appeared atrophied especially in the glomerulosa layer where the cells were decreased in number, and those remaining appeared small with pyknotic nuclei. The thyroid (Fig. 2) acini were lined with high columnar epithelium, and there were only small amounts of colloid in the acini. Some of the fibrous tissue septa between the acini contained large aggregations of densely packed lymphocytes. Striated muscle bundles (Fig. 3) appeared atrophic in many areas with fibrous

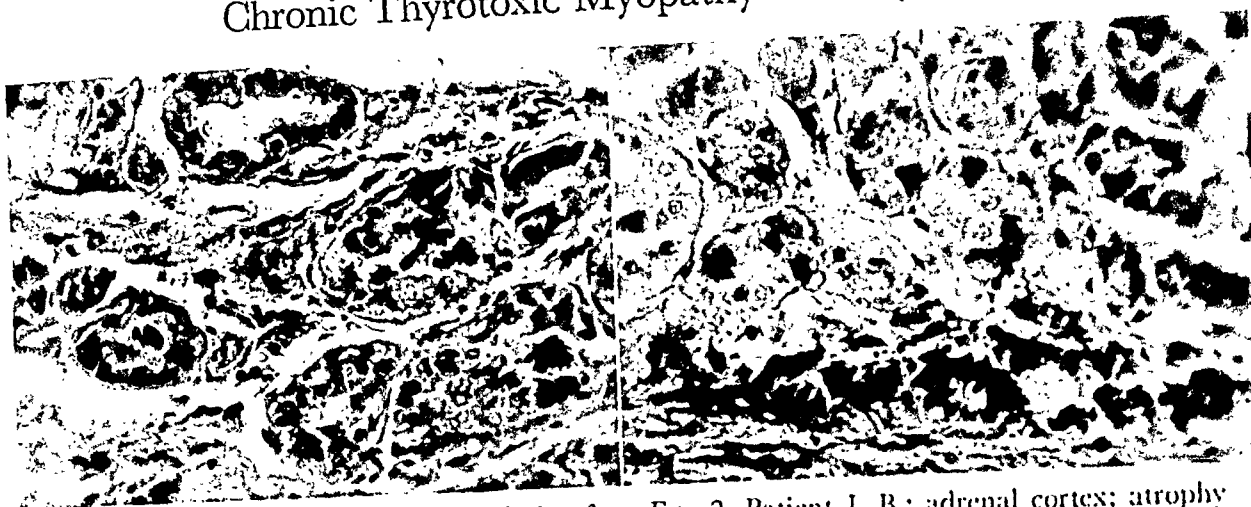


FIG. 1. Patient J. B.; thyroid; hyperplasia of epithelium high columnar cells; marked diminution in colloid content. E M B $\times 225$.

FIG. 2. Patient J. B.; adrenal cortex; atrophy of the zona glomerulosa. Cells are decreased in number and those remaining are small and have pyknotic nuclei. H and E $\times 450$.

replacement of muscle fibers and loss of transverse striations. Occasional areas showed aggregations of lymphocytes. The pituitary was not remarkable.

CASE V. A twenty-two-year-old female with marked weakness of the arms and legs, with atrophy of the muscles of the shoulder girdle, had classical signs and symptoms of thyrotoxicosis. Three weeks after thiobarbital therapy was instituted a four-fold increase in muscular strength had occurred. (Chart 4.)

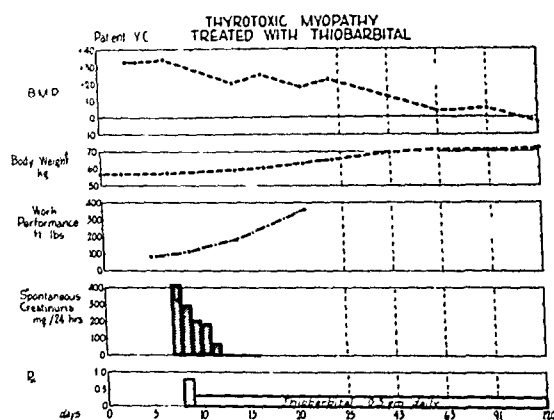


CHART 4.

Y. C., No. M66567, a twenty-two-year-old single housekeeper, entered the Peter Bent Brigham Hospital on June 13, 1944, because of nervousness, weight loss and weakness. She had been in good health until eight months before admission when she had had a severe sore throat and tonsillitis. Following this episode she had felt weak, sweat profusely and lost 10 pounds during the following month. Exophthalmos had then been noted for the first time.

Her most prominent symptom had been the marked weakness of her arms and legs. This progressed so that it had become impossible for her to climb stairs, and she had been unable to raise her arms to comb her hair. Six months prior to admission she had been started on iodine, and there had been a temporary remission in all her symptoms. Two and one-half months before entering the hospital she had stopped the iodine medication. Since then she had lost 30 pounds and had become increasingly



FIG. 3. Patient J. B., skeletal muscle; atrophic muscle bundles with fibrous replacement of muscle fibers. H and E $\times 225$.

more nervous. Sweating had been more marked, and she had noted intolerance to warm weather. There had been considerable muscle weakness especially of the arms and legs with a definite decrease in the size of the muscles. She had had considerable exertional dyspnea and frequent palpitation. Her menstrual periods had always

been regular until two months before admission. At that time she had had an additional period after a seven-day interval.

The patient's past history and family history were non-contributory.

Physical examination on admission showed a well developed and moderately well nourished young woman lying quietly in bed. Her temperature was 98.2°F., pulse 95, respirations 20, blood pressure 140/90 mm. Hg. The skin was warm and moist but of normal texture. There was bilateral exophthalmos, more on the right, with a definite stare, lid lag and convergence defect. Her throat was normal and there was no tremor of the tongue. Her thyroid was considerably enlarged, more so on the right, and there was a definite bruit. Lungs were normal; the heart was not enlarged and sounds were hyperactive. There was a grade III systolic murmur at the left sternal border. No diastolic murmurs were present. The liver edge was just palpable at the costal margin.

There was marked atrophy of the muscles of the shoulder girdle and upper arm, especially the triceps, with marked weakness of the arm especially in extension. There was a fine tremor of the outstretched hands.

Laboratory examination revealed the following: Blood serology was normal. Urine specific gravity was 1.016 with no protein or sugar; spun sediment was clear. Hemoglobin was 14.8 Gm. per cent, hematocrit 38 per cent, and sedimentation rate 14 mm. per hour. White blood count was 6,700 with 70 per cent neutrophils and 23 per cent lymphocytes. Blood urea nitrogen was 5 mg. per cent, total protein 6.5 Gm. per cent, and fasting blood sugar 105 mg. per cent. Stools were negative for occult blood. Venous pressure (method of Burwell) was 115 mm. of water, circulation time (arm to tongue with decholin) was 14 seconds. Urinary 17-ketosteroid excretion was 9.4 mg. per twenty-four hours. On a creatine-free diet her twenty-four-hour urine creatine was 0.42 Gm. Basal metabolic rates before treatment were +33 per cent, +33 per cent and +34 per cent. A chest film showed the heart to be 5 per cent enlarged; there was no substernal thyroid. The work test used consisted in raising a one-pound weight which hung from a rope attached

to a pulley at the foot of the bed. Performance was recorded as the number of times patient could raise the weight by flexing her arm at the elbow. After 1 mg. of prostigmine there was no increase in work performance.

On her 7th hospital day the patient was given a large initial dose of thiobarbital 1.0 Gm. and received 0.3 Gm. daily thereafter. (Chart 4.) There was an immediate and striking reduction in spontaneous creatinuria associated with extremely low creatinine excretion on the day following 1.0 gm. of thiobarbital. (Table III.) It seems probable that this was the result of greatly depleted creatine reserve associated with a rapid retention of creatine in a patient maintained on creatine-free diet. Creatinine values subsequently rose as creatine disappeared from the urine. After one week she improved steadily. Her skin became drier. Her basal metabolic rate dropped to between +18 per cent and +22 per cent at discharge. She gained 7.2 kg. in weight. Before treatment her work performance was 60 with the right arm and 100 with the left. She gradually improved in strength so that by discharge she was able to do 330 on the right and 400 on the left.

The patient was discharged on 0.3 Gm. of thiobarbital daily and was seen in the clinic two weeks later. During that period she gained 4.4 kg. Her gland was smaller, and there was no bruit. Six weeks later her basal metabolic rate was +5 per cent. She had gained 2.0 kg. and was feeling well and strong. She was last seen on November 14, 1944. At that time she was taking 0.1 Gm. of thiobarbital daily, and her basal metabolic rate was -3 per cent. Her weight was well maintained. She felt stronger than she had before the onset of her symptoms and was working in a mill doing moderately hard work. She had no tremor of her hands. Her heart was not hyperactive and no murmurs could be heard. Her muscles were of normal size and strength.

ANALYSIS OF CASES

Age and Sex. The cases which we present and those reported by McEachern and Ross¹¹ are too few to provide reliable statistics on the age and sex incidence of

chronic thyrotoxic myopathy. It is our impression from the data at hand that it occurs in an older age group than does uncomplicated thyrotoxicosis. It also appears that males are frequently affected with a sex ratio different from that reported by Means¹ for uncomplicated thyrotoxicosis in Boston, in which the proportion of males to females is one to four.

Signs and Symptoms. The duration of symptoms in the five patients constituting this report was two to eight months prior to hospitalization. There is no doubt, however, but that symptoms had been present in mild form for a somewhat longer period. In all five patients the presenting complaint was weakness and fatigability. In three, weakness had progressed to such a point that the patients were bedridden and two patients (E. M. and J. B.) were so weak that they were unable to feed themselves.

Weakness of the legs was especially marked. All patients complained of great difficulty in climbing stairs. The most striking muscular atrophy, however, involved the muscles of the shoulder girdle, and in one patient there was winging of the scapula. Involvement of the small muscles of the hands and feet previously noted in patients with chronic thyrotoxic myopathy¹¹⁻¹⁴ did not occur in these patients although it has been observed in a subsequent case. In none of our patients did we observe the fibrillary twitchings which had been seen in several of the patients described by McEachern and Ross,¹¹ nor did we note the facial atrophy described by Ayer, Means and Lerman.¹² One patient (E. M.) presented symptoms of bulbar involvement with thick speech and regurgitation of fluids through her nose.

In all the patients one or more of the signs of thyrotoxicosis were present. In one these were minimal, consisting only of tachycardia and a dry, warm skin. Two had moderate enlargement of the thyroid,

while in two others this was marked. Three of the patients had classical eye signs. These included stare and lid lag in two and definite exophthalmos in a third. In four of the five patients it was possible to make a presumptive diagnosis of thyrotoxicosis by a careful history and physical examination.

Laboratory Data. We observed no clinical improvement in any of our patients after injection of 1.5 mg. of prostigmine. No myograms were made, however. The absence of prostigmine effect is at variance with earlier observations.^{11,15}

In all of our patients there was a significant spontaneous creatinuria ranging from 100 to 590 mg. per twenty-four hours. In all but one patient (G. M.) there was a significant decrease in creatinuria shortly after treatment was instituted. Creatine tolerance tests¹⁶ were done on two patients (G. M. and M. S.), and it was found that there was considerably less creatine retention than normal.

Twenty-four hour urinary 17-ketosteroids¹⁷ were studied in four cases. The two male patients with gonadal atrophy (G. M. and M. S.) had excretions of 8.3 and 8.6 mg. per twenty-four hours respectively, which is a low value when compared to the normal of 12 to 20 mg. for this method. One female patient (E. M.) excreted only 2.7 mg. of 17-ketosteroids per twenty-four hours which is a very low value, whereas another female patient (Y. C.) excreted 9.4 mg. which is normal (9 to 15 mg.). Urinary 17-ketosteroid determinations were not done on patient J. B.

One patient had paroxysmal auricular fibrillation (E. M.), and two had some degree of cardiac enlargement by x-ray (E. M. and Y. C.). Two patients (G. M. and E. M.) showed an abnormally rapid circulation time which decreased to normal after treatment.

Clinical Course. One patient (M. S.) was treated surgically after preparation with

iodine and made a good recovery. Six months postoperatively he showed signs of myxedema which were relieved with thyroid U.S.P. 60 mg.

Two patients (G. M. and E. M.) were treated with thiouracil and one (Y. C.) with a related compound, thiobarbital. The response to treatment was dramatic in all instances. All three patients had a reduction in basal metabolic rate and an increase in strength within two weeks after starting treatment. It is interesting to note that marked objective increase in muscular strength occurred before there was an appreciable gain in body weight. One patient (E. M.) who had been bedridden and unable to feed herself was able to be up and around the ward after one week of treatment with thiouracil.

All four of the patients were completely rehabilitated after treatment of the underlying thyrotoxicosis and were able to take up their occupations which they had dropped at the onset of their symptoms.

The two male patients, despite the fact that they were able to resume their work, felt some residual weakness although there was no visible evidence of muscular atrophy. Because of the gonadal atrophy and low urinary 17-ketosteroid excretion, these patients were given 30 mg. daily of methyl testosterone. On this regimen both noted an increase in muscular strength. In one patient injections of testosterone propionate were substituted with the same result as with methyl testosterone orally. At the time of the testosterone treatment neither of these patients was thyrotoxic.¹⁸

Pathology. One patient (J. B.) with marked atrophy and with little clinical evidence of thyrotoxicosis was admitted to the hospital in a moribund state and died before response to treatment. Pathological examination showed important changes in the thyroid, adrenal, and skeletal muscles. The thyroid (Fig. 1) showed the typical

picture of hyperplasia with large irregular cells and absence of colloid in the acini. The adrenal (Fig. 2) showed atrophy of the zona glomerulosa. The skeletal muscle (Fig. 3) showed many of the changes described by Askanazy.¹⁹ There was marked atrophy with fatty infiltration of the muscles, loss of transverse striations, and replacement of muscle fibers by fibrous connective tissue. In some areas infiltration of lymphocytes was present.

The thyroid removed at operation in patient M. S. showed hyperplasia with iodine involution. It weighed 38.5 Gm. Some of the acini were small, devoid of colloid and lined with high columnar epithelium. Others were larger, filled with colloid and lined by flattened epithelium.

MYASTHENIA GRAVIS AND THYROTOXICOSIS

The combination of myasthenia gravis and Graves' disease is rare. To date six cases have been reported.²⁰⁻²⁵ This association is of considerable interest, since the myasthenia of chronic thyrotoxic myopathy superficially resembles myasthenia gravis and may easily be confused with it. Secondly, it is important to detect thyrotoxicosis when it occurs in the presence of true myasthenia gravis, since the correction of the underlying thyroid disorder may markedly improve the course of the disease.

Case Reports and Observations. We wish to present another instance of the combined diseases (myasthenia gravis and thyrotoxicosis) and also to present a follow-up on a second case previously described.²⁵ Data on the clinical courses of the two patients have been summarized in Table II.

CASE VI. A female, aged fifty-nine, had blurred vision, difficulty in accommodation, ptosis of the eyelids and minimal signs of thyrotoxicosis. Treatment with thiobarbital in the absence of prostigmine was followed by a reduction in basal metabolic rate and increase in

TABLE II
MYASTHENIA GRAVIS AND THYROTOXICOSIS

Patient.....	J. C. Case vi	N. G. Case vii
Sex and age.....	Female, 59 years	Female, 50 years
Duration of symptoms	Eye changes 6 years; 1 month generalized weakness	9 years myasthenia gravis
Thyroid enlargement.	0	+
Other signs.....	Ptosis	Ptosis, exophthalmos, ophthalmoplegia
Tremor.....	0	+
Muscular involvement	Generalized weakness of all muscles; ptosis and diplopia; regurgitation of fluids	Marked generalized weakness, ptosis, diplopia
Hyperreflexia.....	0	0
Initial basal metabolic rate—%	+17	+46
Spontaneous creatinuria mg./24 hours	220	420
Creatinine tolerance test*		
% retention of ingested creatinine	60	22
Cardiac enlargement.	0	+
Prostigmine test.....	Marked improvement	Marked improvement
Treatment.....	Iodine followed by thiobarbital and prostigmine	Iodine followed by subtotal thyroidectomy
Result.....	Definite increase in muscular strength; ptosis disappeared	Four-fold increase of strength and gradual reduction of prostigmine requirement
Basal metabolic rate after treatment—%	—6 (5 months)	+3 (6 years)

* Normal for males 85–100% retention; normal for females 80–95% retention.

TABLE III
URINARY CREATINE AND CREATININE FOLLOWING
THE ADMINISTRATION OF THIOBARBITAL
Patient: Y. C.

Date	Dose of Thiobarbital Gm.	Urinary Creatinine Gm.	Urinary Creatine Gm.
6/18–19	0	0.7	0.4
19–20	1.0	0.7	0.3
20–21	0.3	0.5	0.2
21–22	0.3	0.8	0.2
22–23	0.3	0.8	0.1
23–24	0.3	1.1	0.0
24–25	0.3	0.9	0.0
25–26	0.3	0.5	0.0
26–27	0.3	0.7	0.0
27–28	0.3	0.7	0.0

Patient maintained on a low creatine diet (meat free) throughout this study.

muscular strength. Treatment with prostigmine alone prior to above therapy also resulted in improvement. (Chart 5.)

J. C., No. M66069, an Italian housewife, aged fifty-nine, entered the Peter Bent Brigham

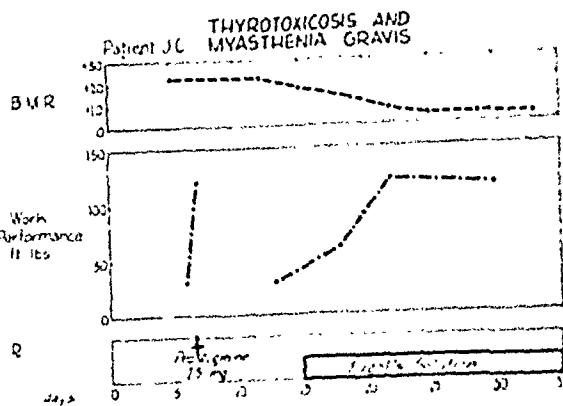


CHART 5.

Hospital on March 20, 1944, complaining of intermittent muscular weakness and pain of two years' duration. She had been well until seven years before admission when she had noted weakness of her left leg on walking. One year later she had begun to have blurred vision with difficulty in accommodating, ptosis of her eyelids and imbalance of her ocular muscles with difficulty in moving her eyes and with diplopia. She had been given prostigmine by her local physician with complete relief of symptoms at first. She had taken the medication sporadically and had been moderately well until three years before admission when she had developed "tolerance" to the drug. Ptosis had continued as a predominant symptom with little oculomotor difficulty. She had had marked weakness and easy fatigability. One month before admission there had been a marked exacerbation of her symptoms. She had developed extreme ptosis. Her legs had become so weak that she had not been able to climb stairs, and finally she had to go to bed. Two weeks before admission she had had difficulty in swallowing for the first time.

There was no past history of intolerance to warm weather, sweating, nervousness or tremor. Family history was non-contributory. Physical examination on admission showed a well nourished, middle-aged woman lying in bed. Movement was difficult and occasioned considerable pain in her muscles. Her temperature was 99°F., pulse 120, respirations 28, blood pressure 160/100 mm. Hg. She spoke clearly. There was no significant lymphadenopathy. There were marked hypertrophic changes in the terminal phalanges of the fingers. Both eyelids showed marked ptosis, more on the left. Extra-ocular movements were weak and un-



FIG. 4. Patient J. C. prior to treatment.



FIG. 5. Patient J. C. twenty-five minutes after administration of 1.5 mg. of prostigmine subcutaneously.

coordinated with inability to look upward with both eyes and weakness of lateral movement on the left. Pupils reacted normally. Fundi appeared normal and the throat was also normal. There was no apparent difficulty in swallowing. Her thyroid was not enlarged, lungs were normal, the heart was not enlarged, sounds were not hyperactive and rhythm was regular and rapid. There was a grade 1 systolic murmur at the base. The abdomen was normal.

There was weakness of all muscle groups but no atrophy. There were no fibrillary twitchings or tremor. Reflexes were hypoactive but equal on both sides.

Laboratory examination revealed the following: Blood serology showed nothing abnormal. Urine showed a specific gravity of 1.012 with no protein and a trace of sugar on admission. Spun sediment contained no red cells, 0-3 white cells, and no casts. Hemoglobin was 14 Gm. per cent, hematocrit 42 per cent, white cell count 5,700 with 69 per cent neutrophils, blood urea nitrogen was 15 mg. per cent, total protein 5.9 Gm., fasting blood sugar 107 mg. per cent, cholesterol 272 mg. per cent, calcium 5.0 m.Eq. per liter, and phosphorus 1.9 m.Eq. per liter.

The stool was normal. Initial basal metabolic rates were +17 per cent and +12 per cent. She excreted 0.59 Gm. of creatinine and 0.22 Gm. of creatine per twenty-four hours. Creatine tolerance test showed retention of 85 per cent of the test dose. X-ray film of the chest showed some coarsening of the lung markings. The heart was transverse in position but not enlarged. Films of the skull showed mild hyperostosis frontalis interna. An electrocardiogram was normal except for the presence of Q_3 . The intravenous glucose tolerance test showed a rise to 365 mg. per cent with a return to normal in two and one-half hours.

Diagnosis of myasthenia gravis (Chart 5) was definitely established by striking improvement with prostigmine therapy and by the marked exacerbation of signs and symptoms after quinine therapy. (Figs. 4, 5 and 6.) Because of persistent tachycardia, warm, moist skin, slight elevation of the basal metabolic rate and the spontaneous creatinuria, thyrotoxicosis was suspected. She was given iodine with a resultant drop in basal metabolic rate from +22 per cent, +22 per cent, and +17 per cent before treatment to +12 per cent in five days, +7 per

cent in eight days and thereafter ± 4 per cent. al pulses dropped from between 80–90 to 80. Her muscle strength (without prostigmine) improved considerably; before starting iodine therapy she was able to raise a 6-lb weight only ten times; nine days after starting iodine she was able to raise it twenty times. Spontaneous creatinuria dropped to 0–0.04 Gm. per twenty-four hours sixteen days after starting the iodine. These facts plus the marked improvement in well-being indicated perthyroidism. Consequently she was started on thiobarbital 0.1 Gm. daily. In addition she was given prostigmine which caused a more marked increase in muscular strength. She was discharged on 120 mg. of prostigmine bromide by mouth and thiobarbital 0.1 Gm.

When seen one month later she was definitely improved. She was less weak and was able to climb stairs and to comb her hair, which she could not do before coming to the hospital. She had no ptosis or diplopia. Basal metabolic rate was ± 9 per cent.

Five months later she did not appear to be doing well; her appetite was poor and she had lost 15 pounds. On 150 mg. of prostigmine daily she had no ptosis but could climb stairs only with difficulty. She complained of being cold most of the time, and her skin was dry and cool. Basal metabolic rate was -6 per cent. Prostigmine was raised to 180 mg. daily, and thiobarbital was stopped.

The patient was last seen August, 1945. At that time she was considerably stronger and able to get around without difficulty, and she had reduced her daily intake of prostigmine to 90 mg. from the earlier requirement of 180 mg. daily. The thyroid gland was firm and twice normal size. There was no evidence of thyrotoxicosis, her basal metabolic rate being -8 per cent.

CASE VII. A female, fifty years of age, received prostigmine therapy for myasthenia gravis over a period of nine years with considerable benefit. During this period thyrotoxicosis was suspected but never proved. Following the administration of iodine, there was a reduction in basal metabolic rate and creatinuria. Following subtotal thyroidectomy a striking improvement in muscular strength occurred, and a great decrease in prostigmine requirement was noted.

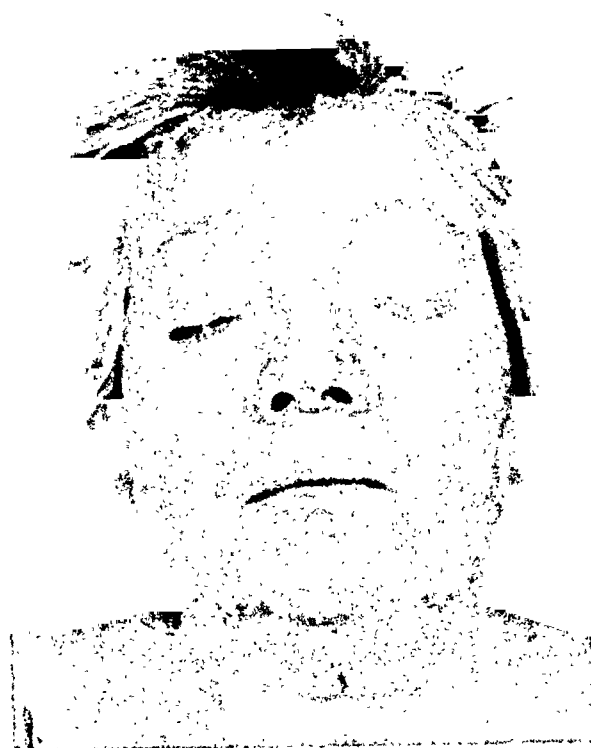


FIG. 6. Patient J. C. following the administration of quinine sulfate (1.2 Gm. total dose) given over a period of ten hours.

N. G.,* No. M145931, a negro school teacher, fifty years of age, was first seen at the Johns Hopkins Hospital on February 5, 1929, complaining of double vision and drooping of the eyelids for the previous three months.

Physical examination showed a poorly nourished colored woman with tachycardia and moist skin. There was marked ptosis of both eyelids, left external strabismus and bilateral exophthalmos. The thyroid was not enlarged, but an audible bruit was present. The heart was enlarged, and there was an apical presystolic rumble. Skeletal muscles contracted strongly at first but fatigued easily. Blood, urine and spinal fluid were normal. Basal metabolic rate ranged between ± 10 per cent and ± 36 per cent. During subsequent admissions she complained of increasing weakness of the extremities and trunk with difficult breathing. In November, 1930, she received x-ray treatment over the thyroid gland with some improvement in strength. In September, 1937, she was started on prostigmine, and there was considerable improvement. Treatment could not be continued, however,

* This case was previously reported by Thorn and Tierney.²⁶

because of diarrhea and increased menstrual flow. In July, 1938, she was seen again because of an exacerbation of her symptoms. At this time she had a five-week history of increased nervousness, tremor of her hands, sweating, palpitation and weight loss despite increased appetite. She had marked weakness of her arms and legs so that she was unable to walk without assistance. Physical examination showed, in addition to the findings previously noted, increased nervousness, exophthalmos, bilateral ptosis and ophthalmoplegia. The thyroid was enlarged. There was marked weakness of her skeletal muscles and a coarse tremor. Her basal metabolic rate was $+46$ per cent. Serum cholesterol was 192 mg. On a creatine-free diet the spontaneous urinary creatine excretion was .420 Gm. per day. In the creatine tolerance test she retained 22 per cent of the test dose. After these preliminary studies she was given Lugol's solution. Her creatine excretion fell to .050 Gm. per day, and 59 per cent of the oral dose of 2.61 Gm. of creatine was retained as compared to 22 per cent before iodine therapy. Her basal metabolic rate decreased slightly during this period. After twenty-five days of iodine treatment a subtotal thyroidectomy was performed. Postoperatively there was general improvement in strength, and she was soon able to walk even in the absence of prostigmine therapy, but the ptosis and ophthalmoplegia did not change appreciably. With prostigmine treatment after operation the ptosis disappeared completely, and she had sufficient strength to return to work.

In the six and one-half years since operation her prostigmine requirement has steadily dropped so that at the present time she takes less than 15 mg. per day to maintain her strength. During this period she has been able to continue her work as a school teacher, although there is still residual weakness of her face and skeletal muscles on sustained effort.

Analysis of Cases. The two patients (J. C. and N. G.) with myasthenia gravis who developed thyrotoxicosis were females, aged fifty-nine and fifty years, respectively. One had had symptoms of myasthenia gravis for six years and symptoms of hyperthyroid-

ism for one month. The other had been followed for nine years before a diagnosis of thyrotoxicosis was definitely established. Both were typical cases of myasthenia gravis with ptosis, oculomotor weakness and moderate generalized weakness. Both responded to prostigmine. In one patient signs of thyrotoxicosis were minimal and consisted only of slight thyroid enlargement, tachycardia and warm moist skin. The other patient had an enlarged gland, with exophthalmos and tremor of hands. Neither patient showed striking muscular atrophy, and weakness was of the myasthenia gravis type, i.e., it became more marked on sustained effort. There were no fibrillary twitchings. Both patients had elevated basal metabolic rates of $+17$ and $+46$ per cent, respectively. Both had spontaneous creatinuria of 220 and 420 mg. per twenty-four hours, respectively. Both showed abnormally high creatine excretions following the administration of creatine. On test doses of iodine there was a definite increase in strength of muscles, and there was a drop in the spontaneous creatinuria which does not occur in uncomplicated myasthenia gravis treated with iodine.²⁵ One patient was treated with thiobarbital and the other had a subtotal thyroidectomy performed. In both there was a gradual increase in muscular strength. The prostigmine requirement in the one patient followed for six and one-half years gradually declined so that at the end of that period she was taking occasional doses of 15 mg. per day.

COMMENTS

In these patients with striking myopathic changes in thyrotoxicosis it is of interest to speculate on what particular factors or mechanisms conditioned the response of these individuals in such a way that the myopathic changes predominated in the manifestations of thyrotoxicosis.

In our two patients with myasthenia gravis the primary disease was markedly aggravated by thyrotoxicosis. This has also been reported in periodic paralysis.⁶ It has been suggested that an occult primary myopathy underlies many cases of thyrotoxic myopathy. If this were the case, one might expect some evidence of the primary neuromuscular disease to persist following correction of the complicating thyrotoxicosis, but this has not been observed in our five patients.

There is some evidence that an associated disturbance of steroid hormone production occurs in these patients, as indicated by (1) low urinary excretion of 17-ketosteroids in several patients, (2) testicular atrophy in the two males, and (3) the degenerative changes in the adrenal demonstrated in patient J. B. It has been found experimentally that normal rats, when injected with 1 mg. of thyroxin daily for fifteen days, exhibit striking increase in adrenal and testicular weight despite generalized weight loss and wasting.²⁶ This suggests that the steroid hormone requirement may be increased in thyrotoxicosis. That a deficiency of these hormones conditions an over-all unfavorable response in thyrotoxicosis is suggested by the following:

1. Adrenalectomized and/or castrate animals treated with thyroxin have a much higher mortality rate than normal animals treated with the same dose of thyroxin.²⁶
2. Administration of adrenal cortical and gonadal hormones increases the survival rate of normal adrenalectomized and castrate animals given thyroxin.²⁶
3. It is well known clinically that patients with adrenal insufficiency, both primary and secondary, tolerate thyroid administration very poorly.^{1,27}

These factors most certainly have a marked direct effect on muscle. Hertz et al.²⁸ have shown clearly that testosterone propionate has a marked nitrogen retaining

effect even in the presence of thyrotoxicosis. That adrenal cortical hormone has a direct effect on the metabolism of muscle tissue has been clearly shown in the hexokinase studies of Cori et al.²⁹ The hypothesis that the combination of thyrotoxicosis and steroid hormone deficiency can cause marked myopathy certainly appears reasonable.

Creatinuria and a decrease in the creatine and phosphocreatine content of the muscle are common findings in thyrotoxicosis.³⁰ The fact that phosphocreatine is an intermediate in the cycle of energy release in the muscle strongly suggests that the clue to the mechanism of thyrotoxic myopathy may be found in careful study of creatine metabolism in these patients. Many of the steps in the synthesis and utilization of creatine have been elucidated in recent years by a combination of experiments on intact animals and tissue slices and with isotopes of nitrogen and hydrogen. Glycocyamine, the unmethylated creatine, is formed in the kidney by the transfer of the amidine group from arginine to glycine. (Fig. 7.)³¹ This synthesis can be increased by feeding glycine or arginine.³² The glycocyamine formed is methylated in the liver by transfer of a methyl group from the methyl pool (chiefly choline) by way of methionine. (Fig. 8.)³³ In the muscle the creatine is phosphorylated to phosphocreatine (Fig. 9)²⁴ which in turn replenishes the phosphate groups of adenylyl phosphate to form adenosine triphosphate, the breakdown of which has the closest known energy linkage with the actual shortening process of the muscle fiber. In this step creatine phosphate appears to form creatinine, which is eliminated from the body in the urine at the rate of about 2 per cent of the total body creatine per day.³¹

In thyrotoxicosis there are three possible mechanisms for the creatinuria:

- (1) *Increased Synthesis of Creatine in the Body.* In two patients with uncomplicated thyro-

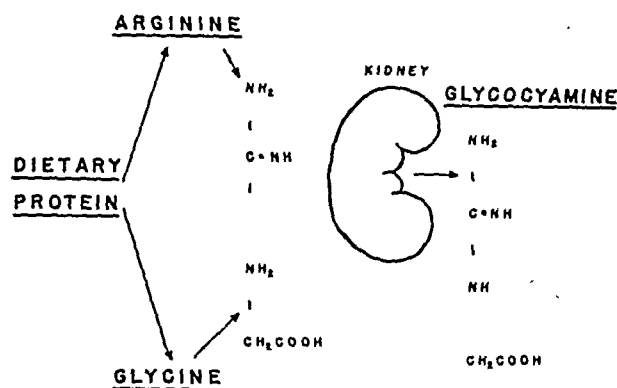


FIG. 7.

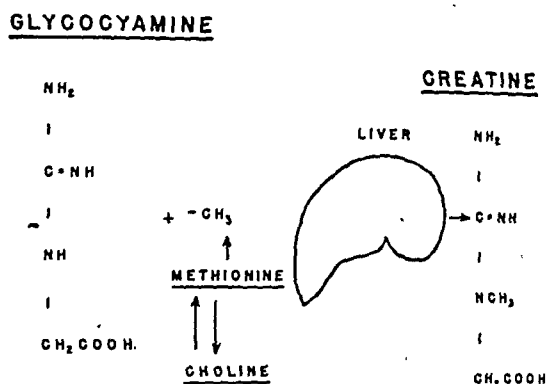


FIG. 8.

toxicosis twenty-four-hour glycocyamine excretion was measured and this was not increased. Although methylation can proceed at a rapid rate, it has been shown that where there is increased synthesis of creatine, as in treatment with methyl testosterone, there is increased glycocyamine excretion.³⁵

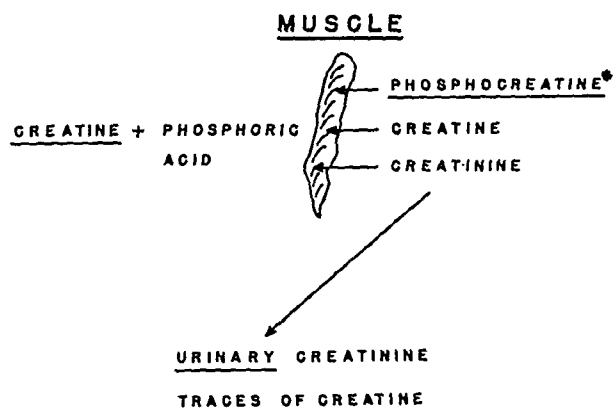


FIG. 9.

(2) Direct Loss of Creatine from the Muscle.

There is no doubt that this is an important source of urinary creatine. In a rat given thyroxin at the rate of 2 mg. per day the loss of creatine in the urine divided by the weight loss showed a creatine concentration of the order of magnitude of muscle.²⁶ In chronic thyrotoxicosis, however, the muscle stores of creatine alone are probably not sufficient to account for the prolonged creatinuria.

(3) *Failure of Storage and Utilization of Creatine in the Muscle.* That this is a factor in operation in thyrotoxicosis is clearly demonstrated by the decreased creatine tolerance test and by the clinical studies of

Wilkins and Fleischmann.³⁶ A high percentage of a dose of creatine which can be stored easily by a normal person is excreted in the urine of most patients with thyrotoxicosis.³⁷ Since it appears that creatinine is formed from phosphocreatine, the decreased creatinuria so often associated with creatinuria suggests that this failure in storage may result from a failure of phosphocreatine synthesis. In short, the creatinuria of thyrotoxicosis may represent a combination of increased muscle breakdown which is non-specific and parallels the negative nitrogen balance, and a specific failure in creatine utilization and storage.

There appears to be little correlation between the severity of the myopathy and the extent of creatinuria. (Table I.) In the four patients studied the spontaneous urinary creatine ranged between 100 and 590 mg. per day. There did appear to be a much greater spontaneous creatinuria in the two female patients than in the two male patients. (Table I.)

It does not appear that chronic thyrotoxic myopathy can be explained on the basis of a simple exaggeration of the usual creatine metabolic defect in thyrotoxicosis, since there is no striking increase in creatine excretion in these patients over that seen in uncomplicated thyrotoxicosis. It is suggested that the defect may be one rather in the direction of failure to maintain adequate synthesis to meet the abnormal demands. This point requires further investigation.

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Disturbance in Salt and Water Metabolism in Hypertension*

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EVIDENCE that the adrenal cortex may be concerned in the development or maintenance of essential hypertension in man has previously been reported.^{1,2} It is of interest that drastic reduction in sodium intake may result in a decline in blood pressure in hypertensive patients,³ possibly through the established influence of the adrenal cortex on salt and water metabolism.

In the course of clinical studies aimed at extending observations on the rôle of sodium in hypertensive vascular disease, it was noted that patients with hypertension differed from control subjects in their response to sodium restriction. It is the purpose of this study to report these findings.

EXPERIMENTAL

All studies were carried out on the wards of the Presbyterian Hospital. Patients with uncomplicated hypertensive vascular disease were included only if the arterial pressure consistently exceeded 140/90 mm. of mercury and in the absence of cardiac pain or insufficiency, renal or cerebral complications or fever. All patients were free of albuminuria, showed normal phenolsulfonephthalein excretion and urine concentration tests, and in all instances the venous pressure was within normal limits. Control subjects included afebrile convalescent patients and healthy volunteers under hospital observation without evidence of cardiac, renal or endocrine disease and with repeatedly normal blood pressure readings.

Both groups were comparable in sex distribution and included as wide an age span as possible. To eliminate any cyclic changes in fluid balance, experiments on female subjects were carried out one to two weeks after the last menstrual period. Thin and obese patients were included in both series studied. All subjects were weighed daily on the same scales before breakfast and before bowel movement.

Sodium chloride was administered by mouth using weighed salt shakers, additional supplements being given in some instances in the form of enteric-coated tablets. Identical salt-poor daily menus were prepared. Repeated direct analyses of aliquots taken from an entire day's cooked diet gave values of between 0.25 to 0.35 Gm. of sodium or considerably less than 1 Gm. of sodium chloride per day. It was found that such diets were not difficult to prepare, permitting the inclusion of sweet butter, salt-free bread, two daily servings of meat and small portions of cream, as well as sugar, fruits and vegetables. These salt-poor diets yielded 1,700 to 2,200 calories and 70 to 80 Gm. of protein, and did not include special ingredients such as dialyzed milk.

Under different conditions of activity and environmental temperature, and with different amounts (4 to 10 Gm.) of added sodium chloride, twelve control and twelve hypertensive subjects were placed on constant food and fluid intake. Paired observations, using one control and one patient

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TABLE I
RESULTS OF SODIUM RESTRICTION IN CONTROLS AND HYPERTENSIVES

RESULTS OF SODIUM RESTRICTION																		
	No.	Age	Sex	Ambulation before and during Study	Antecedent NaCl Intake Gm.	Weight					Before and after 24 hrs. Sodium Restriction							
						Day 1	2	3*	4	5	Weight Change Kilos	Hematocrit Change % Cells	Total Serum Protein Change Gms./ 100 cc.	CO ₂ Content (Milliequiv./Liter)	Serum Chlorides As NaCl cc.	Urine Volume Change cc.	Urine Chlorides Meq./24 Hrs. as NaCl.	
Normal Subjects	1	48	M	quiet ambul.	5	76.38	76.66	76.42	75.38		-1.04							
	2	15	F	bed	5	74.70	74.72	74.73	74.10	74.70	-0.63	+1	0	25.5-26.0	102.8-101.2	+370	130-96	
	3	34	M	average amb.	10	73.06	73.10	73.18	71.58	72.86	-1.60	+1	+0.3		103.1-102.2	+650	154-96	
	4	23	F	" "	7	70.14	70.00	70.03	68.84	69.72	-1.19	+1	+0.1	27.6-28.0	98.9-96.3	+475		
	5	33	F	" "	5	57.14	57.04	56.86	55.54	56.63	-1.32				100.7-100.8	+620	123-62	
	6	34	M	quiet ambul.	6	72.10	72.08	72.00	71.21	72.04	-0.69						+645	
	7	55	M	" "	5	59.69	59.96	60.55	58.70	60.07	-1.85						+960	
	8	87	F	bed	5	47.43	47.65	47.87	47.32	47.43	-0.55						+300	
	9	51	M	quiet ambul.	4	63.00	62.70	62.70	62.73	63.25	-0.55	-1	-0.3	27.7-28.4	96.5-97.2	+250	77-49	
	10	48	F	average amb.	8	65.63	65.76	65.93	64.92		-1.01						+500	
	11	20	F	quiet ambul.	5	49.74	49.24	49.35	48.66	49.31	-0.69	+2	+0.2	27.5-26.6	100.1-97.5	+220		
	12	45	F	" "	5	69.16	69.28	69.51	68.51	68.90	-1.00							
mean = -1.01																		
Hypertensives	1	44	F	average amb.	7	62.12	62.42	62.70	62.22		-0.48	-2	-0.2	24.2-24.4	104.8-105.2	+300	51-52	
	2	45	M	quiet ambul.	7	59.17	58.91	58.85	58.84	58.56	-0.01	+1	+0.1	27.8-27.8	105.6-99.5	+100	111-61	
	3	22	M	bed	8	50.11	50.10	50.05	50.10		+0.05	+1	+0.1	26.1-27.9	98.0-95.2	-75		
	4	44	F	quiet ambul.	6	68.52	68.48	68.36	68.15		-0.21		+0.1		104.3-103.3	+100	80-38	
	5	44	F	" "	9	65.00	64.75	64.85	64.53	64.40	-0.32			29.3-28.9	103.2-101.3	+400	148-46	
	6	45	M	average amb.	5	60.50	60.66	60.60	60.13	60.34	-0.47	-1	-0.2	28.1-28.4	101.8-100.0	-160		
	7	55	F	quiet ambul.	8	51.77	51.93	51.61	51.43		-0.18	0	+0.2	27.1-27.5	100.7-99.6	+160	71-56	
	8	46	M	average amb.	7	58.61	58.30	58.36	58.31	58.19	-0.04						83-45	
	9	46	F	bed	5	50.64	50.50	50.24	50.40		+0.14					-275		
	10	61	F	quiet ambul.	5	50.70	50.95	51.25	50.80		-0.45					+75		
	11	63	F	average amb.	5	62.70	62.76	62.86	62.69	62.80	-0.17					+200	77-45	
	12	36	F	quiet ambul.	4	58.00	57.85	57.90	57.67	57.75	-0.23	-1	+0.3	26.6-27.3	101.5-99.5			
mean = -0.198																		

* Start of 24 hr. sodium restriction.

with hypertension, were made whenever possible. After two days on a constant regimen, the added sodium chloride was withdrawn for twenty-four hours (beginning with breakfast on the third day), but without other change in activity, diet or fluid intake. Sodium chloride administration was resumed on the morning of the fourth day.

RESULTS

In association with rigid sodium restriction for twenty-four hours, a conspicuous weight loss occurred in all of the control non-hypertensive group which was not apparent in any of the hypertensive subjects (Table I, Fig. 1.) After one day without

added salt, the mean weight loss of the control group was 1.0 kg. as compared to 0.2 kg. in the patients with hypertension. Calculation of the standard error of the differences proved these values to be statistically significant. No matter whether a control subject lay in bed with little clothing on a cool day (mean temperature 59°F.), or a warmly clothed hypertensive patient exercised vigorously on a hot day (mean temperature 81°F.), all of the control subjects lost more than 0.55 kg., whereas weight loss among the hypertensive series never exceeded 0.48 kg.

In addition, the control group exhibited a diuresis after salt withdrawal, whereas the hypertensives showed much smaller varia-

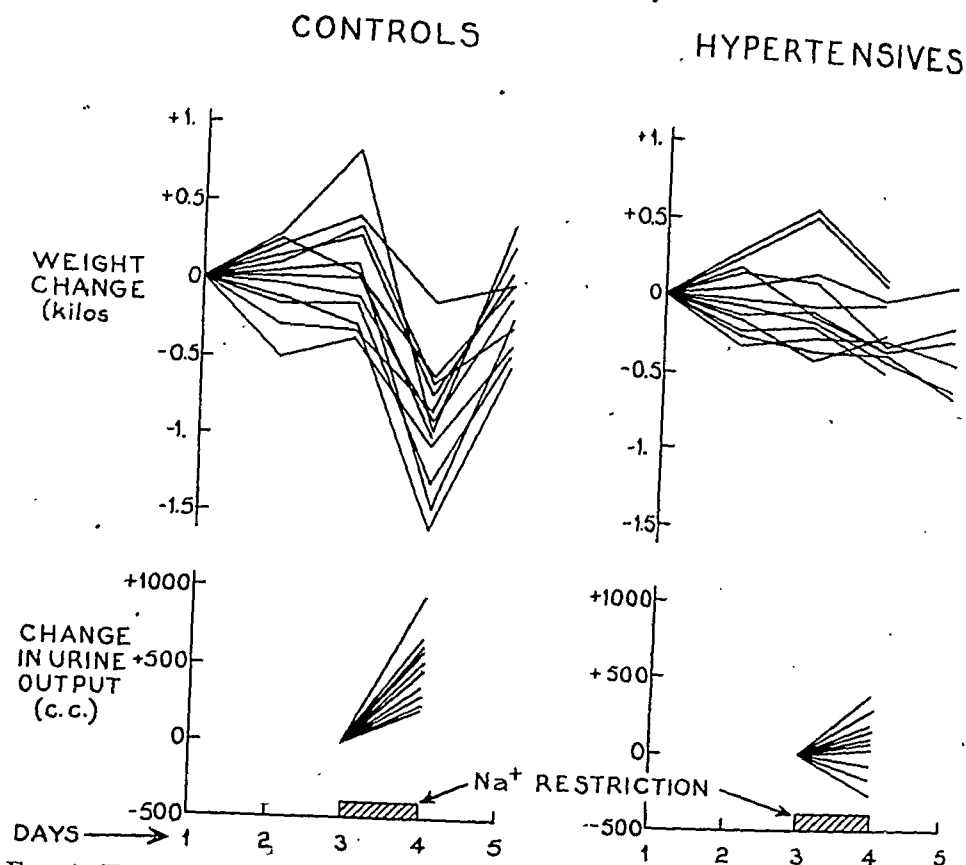


FIG. 1. The effect of salt restriction on weight and urine output in control and hypertensive subjects.

tions in urine output. Furthermore, several in the control group noted increased sweating, insomnia or slight weakness toward the end of the twenty-four-hour period of sodium restriction, none of which symptoms were noted by patients with an elevated blood pressure. Two control subjects, who were later placed on salt restriction for forty-eight hours and developed the above symptoms to a greater extent on the second day, also complained of subjective disturbances similar to those described by McCance in salt-depleted normal individuals.⁴ On the other hand, it was shown repeatedly that hypertensive patients could tolerate weeks of the low sodium diet without discomfort of any kind.

Urine sodium determinations were made on twenty-four-hour samples in two control subjects and in two hypertensives, before and after salt restriction was instituted, on the same day in both pairs, and after identical menus and sodium intake. Following the withdrawal of salt, the sodium values in the

urine decreased to the same extent in both instances.

Urine chlorides, usually decreased in control and hypertensive subjects. Significant changes in hematocrit, total proteins, serum CO_2 and chloride determinations were not observed. Blood pressure levels were not materially affected by the twenty-four-hour period of salt withdrawal.

Calculation of sodium and chloride clearances (UV/P) in two control subjects and two hypertensive patients showed little change in the non-hypertensive individuals following salt restriction but a definite reduction in clearance values in the patients with elevated blood pressure.

COMMENTS

It has been shown that non-hypertensive subjects respond differently to the rigid withdrawal of sodium from the diet as compared with a group of patients with uncomplicated hypertensive vascular disease. Regardless of the amount of activity

or of the antecedent salt consumption, a drastic reduction of sodium intake in control subjects was followed by an immediate and significant loss in weight attributable in part to an associated diuresis. If this was carried much beyond a twenty-four-hour period, a regular pattern of symptoms appeared. Patients with essential hypertension, on the other hand, showed minimal weight change, failed to exhibit a diuresis and were symptom-free.

The decrease in weight in the control group was not entirely explained by the alteration in urine output. As several subjects noted increased perspiration, it is possible that changes in sweat production may have been responsible in part. Preliminary observations suggest that the urine sodium and chloride values were largely influenced by the reduction in sodium and chloride by mouth, rather than by the changes in urine volume, but the net result was a decrease in sodium and chloride clearances in two hypertensive patients studied as compared to minimal change in normal subjects. Whether or not a shift of sodium into cells accompanied the diuresis observed in control subjects remains to be seen.

The mechanism involved in this difference in behavior remains obscure. It is conceivable that the defect is purely renal in origin, secondary to changes produced by hypertension. However, with the exception of the nephrotic syndrome, in which reabsorption is augmented, most kidney disorders involving the tubular elements are associated with a decreased capacity for reabsorption. The effects of a low sodium diet on glomerular filtration and tubular function must be further elucidated.

The inability of hypertensive patients to lose weight and fluids in response to sodium restriction is consistent with the view that the adrenal cortex may be implicated, since the tubular reabsorption of salt and water is

known to be influenced by desoxycorticosterone. Furthermore, it has been repeatedly demonstrated that the arterial blood pressure may rise in normal subjects¹ and may exceed normal limits in a considerable number of patients with Addison's disease in the course of treatment with desoxycorticosterone esters.⁶⁻¹¹ Not only has it been suggested that the abnormal liberation of certain adrenal cortical steroids may be concerned in the etiology of hypertension,² but recent studies have shown that sodium chloride appears essential for pressor and certain other activities of desoxycorticosterone when administered to rats rendered nephritic with nephrotoxic serum.⁵

CONCLUSIONS*

1. Observations have been made on twelve control subjects and twelve patients with uncomplicated hypertensive vascular disease following the rigid withdrawal of sodium chloride for twenty-four hours.
2. Despite an otherwise constant regimen, sodium restriction was followed by significant weight loss and increased urine output in control subjects which was not evident in hypertensive patients, regardless of variations in environmental temperature and physical activity.
3. A disturbance in salt and water metabolism exists in hypertensive vascular disease as judged by the abnormal response to the abrupt and rigid restriction of sodium in the diet.
4. It is suggested that this difference in response may be referable to primary renal changes or, more likely, to changes in the kidney mediated by the adrenal cortex.

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Thiouracil in Angina Pectoris*

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ALTHOUGH the value of total thyroidectomy for severe angina pectoris has been generally recognized, the procedure has fallen into disuse because of the initial risk, subsequent complications and likely myxedema. Accordingly, when the anti-thyroid agent, thiouracil, was introduced, one of the earliest suggestions for its use in other than thyrotoxic states was as a substitute for thyroidectomy in the control of angina pectoris. Here it was expected that a reversible, risk-free chemical thyroidectomy might be performed with results at least comparable to those formerly attained surgically. That this appears to be a valid assumption is attested to by the report of Raab,¹ in which seven of ten patients with angina responded favorably, and that of Ben-Asher,² with eight patients successfully treated.

To determine whether thiouracil is consistently active in this respect, its ability to depress a normally functioning thyroid gland and to lower the basal metabolism must be established. Then, too, toxic reactions from the drug must be infrequent enough not to eliminate too many patients from treatment over an extended period of time. Finally, in this preponderantly subjective disease, a thoroughly objective, skeptical attitude must be adopted by the investigator in evaluating reported changes in the patient's condition.

While there is ample evidence of the thyroid depressant effect of thiouracil in normal animals and in humans with thyrotoxicosis, little data are available demon-

strating a similar action on the normal human thyroid. In the thyrotoxic state positive action becomes manifest in an average six to eight weeks, but in the normal it is reasonable to expect a longer time to elapse if the tightly organized pituitary-thyroid relationship is to be disrupted. Astwood has observed the development of myxedema in normal humans after at least five months' continuous administration of the drug. Similar observations have not been reported by any one else, so that this basic question will be answered only as experience accumulates.

Toxic reactions from thiouracil have an unpredictable incidence of 10 to 15 per cent. These consist mainly of drug fever, skin eruptions, leukopenia and agranulocytosis, and their occurrence appears unrelated to dosage or duration of therapy. However, the risk is not too great if a close watch is kept through repeated blood counts, and the patient is instructed to report promptly any untoward development. Except in the case of the skin reactions or leukopenia, when the drug may be restarted at a lower dosage level without recurrent reaction, drug fever and agranulocytosis eliminate the patient from further treatment.

It is quite obvious that in angina, in which so much of the disturbance is subjective, care must be exercised in evaluating reports of improvement which may be wishfully inspired. Interruption of treatment at intervals, with substitution of placebos, is perhaps the best method of testing the validity

* From the Department of Medicine, Harper Hospital, and Wayne University College of Medicine. Thiouracil and propyl-thiouracil were supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Inc., Pearl River, New York.

of the improvement, though this may invite toxic drug reactions. Oxygen deprivation as between the two methods, the former appears the more practical. Spontaneous improvement must also be thought of in evaluating the results of therapy but there is no way of tagging this factor so that it must stand as a negative quantity in any final summation of results. One final point worth remembering is that the patient with severe angina, for whom a trial of thiouracil may be especially indicated, will not long maintain his enthusiasm for any method of treatment if genuine relief is not obtained. With these guiding views, studies were made on a group of eight patients with angina, five of whom were observed for a period of approximately one year. In two the disturbance was mild, in two it was moderately severe and in the remaining four severe. On beginning treatment the action of the drug with its possible ill effects was fully explained and the patients instructed to report promptly any ill effects. Basal metabolic rate determinations and blood counts were at first repeated every two weeks and later every four weeks. The initial dose of thiouracil was either 0.4 or 0.6 Gm. daily, divided into two or three equal doses. This was reduced to 0.3 or 0.2 Gm. daily as soon as there was any improvement. Patients were permitted to continue taking nitroglycerin as necessary and were also allowed to use a mild sedative when unable to sleep.

CASE REPORTS

CASE I. S. G., a fifty-two-year old white male, had had attacks of chest tightness and pain radiating down the left arm for almost a year. He was able to continue work as a tailor as long as he took from four to six tablets of nitroglycerin daily. During the month previous to his first visit, however, the attacks of pain became more frequent and severe and were no longer adequately controlled by nitroglycerin.

CASE II. M. A., a fifty-nine-year old white female, developed chest pain and tightness with shortness of breath on exertion ten months previous to her visit in April, 1944. Hypertension had been present for several years. She was somewhat obese, the blood pressure was 168/90 and there was a grade 2 retinopathy. The thyroid showed bilateral nodular enlargement without evidence of toxicity. The heart sounds were forceful but there were no murmurs. She failed to improve during the next ten months in spite of loss of eighteen pounds and the use of aminophyllin and sedation.

In March, 1945, the basal metabolic rate was plus 1 per cent, the blood cholesterol 245 mg. per cent, and the chest x-ray showed no increase in heart size. The EKG showed left axis deviation, small Q₁ and negative T₃.

Thiouracil, 0.2 Gm. three times daily, was started and the patient advised to continue using nitroglycerin as necessary. Little improvement was noted during the following three months. The basal metabolism readings during this period were minus 11, 6, 18 and 12 per cent. The patient failed to return for further observation.

Comment. In this instance of severe angina, thiouracil administered continuously for three months in a dosage of 0.6 Gm. daily failed to produce any improvement. The lowest basal metabolism level attained was minus 18 per cent.

His physical examination revealed no distinctive abnormalities. The blood pressure was 150/90, the heart size was normal and there were no murmurs. The EKG showed left axis deviation, small Q₂, flattened T₂ and inverted T₃, and the precordial leads were normal. The initial basal metabolism was minus 15 per cent on March 21, 1945.

Thiouracil, .2 Gm. three times daily, was started and the patient advised to continue using nitroglycerin as necessary. Little improvement was noted during the following three months. The basal metabolism readings during this period were minus 11, 6, 18 and 12 per cent. The patient failed to return for further observation.

His activity was greatly limited and he remained closely confined to his home.

Comment. This patient with mild angina failed to improve after six weeks' continuous administration of thiouracil at the rate of 0.6 Gm. daily. The lowest basal metabolism attained was minus 2 per cent.

CASE III. B. W., a forty-six-year old white male, noted increasing shortness of breath, tightness of the chest with numbness in both arms, and exhaustion following almost any form of exertion during the two years preceding his first visit.

Physical examination was negative, the blood pressure 140/90 and no heart murmurs were heard. X-ray study of the chest showed the heart size at the upper limits of normal. The EKG showed left axis deviation with slurring and notching of QRS and Q_1 , Q_3 and QCF_5 present.

A regimen of lessened activity, small meals, no tobacco and aminophyllin and sedatives was followed for four months without improvement. In August, 1945, thiouracil, .2 Gm. twice daily, was started, the initial basal metabolic rate being minus 6 per cent. Subsequent determinations at monthly intervals were plus 2, minus 8, 16, 24, 15, 10, 16, 0, 9, 20 and 8 per cent. Improvement was reported at the end of four weeks and the tightness in the chest disappeared after eight weeks. At this point the thiouracil was reduced to .1 Gm. three times daily.

At the end of four months' treatment the basal metabolic rate was minus 24 per cent and the patient's face was puffed, he was sluggish and complained of sensitivity to cold. The blood cholesterol was 324 mg. per cent. The chest tightness and numbness in the arms had returned but this gradually disappeared during the next two weeks on a reduced dose of .1 Gm. thiouracil twice daily. Treatment was continued for another four months, then terminated. The patient had been entirely symptom-free during this latter period as well as during the subsequent four months' interval without medication. No change was found in the EKG or chest x-ray at this time.

Comment. This patient with moderately severe angina, starting with an initial basal metabolism of minus 6 per cent, showed

improvement at the end of eight weeks on 0.4 Gm. thiouracil daily. After four months' treatment the basal metabolic rate dropped to minus 24 per cent and myxedema developed. Symptoms returned at this time but disappeared promptly on a lowered dosage of 0.2 Gm. thiouracil daily which was continued for four months. He has remained symptom-free during the subsequent four months without medication.

CASE IV. M. C., a fifty-two-year old white male, had recovered from an acute anterior myocardial infarction in 1941 which had been preceded by several months of precordial tightness brought on by exertion, emotional disturbance and exposure to cold. He remained symptom-free until January, 1943, when the chest tightness returned. At this time the EKG showed absent R in lead IVF with negative T and the chest x-ray showed no increase in heart size.

The attacks were mild and irregular until December, 1944, when they increased in severity and frequency, requiring six to eight tablets of nitroglycerin daily for control. Then, following a train wreck, pain and tightness were markedly aggravated and even thirty to forty tablets of nitroglycerin daily failed to give sufficient relief to allow him to venture out of the house. Repeated EKG studies failed to show any change from previous tracings.

Early in June, 1945, thiouracil, .2 Gm. three times daily was started. The initial basal metabolic rate was plus 5 per cent. There was considerable gastric distress from the drug during the first two weeks, but no other reaction was noted. Little improvement occurred during the first eight weeks' treatment, the basal metabolism readings in this period being 0, minus 22, 5 and 13 per cent. In another two weeks, however, there was considerable improvement; he was able to go out for short walks and required only two or three tablets of nitroglycerin daily. The basal metabolism was now minus 16 per cent and the thiouracil was reduced to 0.4 Gm. daily.

At the end of five more weeks the patient was quite comfortable although the basal metabolic

rate was minus 3 per cent. Thiouracil was discontinued for one week and there was a prompt return of symptoms and the basal metabolism rose to plus 7 per cent. Medication was resumed and the distress was relieved in three to four days.

During the next ten weeks the patient remained quite comfortable, requiring only an occasional tablet of nitroglycerin following considerable exertion. The basal metabolism readings during this period were plus 6, minus 9 and plus 11 per cent. The thiouracil was discontinued at this point because the patient was leaving the city. After a little over six months' treatment there was considerable improvement and the patient had gained ten pounds.

Shortly after his arrival in California the attacks of distress recurred and his attending physician prescribed 3 gr. aminophyllin with $\frac{1}{4}$ gr. phenobarbital four times daily, with nitroglycerin to be taken as needed. He remained symptom-free on this regimen for four months and has been free of all discomfort without any medication since his return home three months ago.

Comment. This patient with severe angina coming on several years after a healed myocardial infarction showed improvement after ten weeks of thiouracil, 0.6 Gm. daily. The initial basal metabolic rate was plus 5 per cent and a level of minus 16 per cent was noted at the time of improvement. Symptoms recurred when the thiouracil was discontinued, and disappeared shortly after it was restarted. There was marked improvement after six months' therapy and a subsequent recurrence was controlled with aminophyllin and sedation given over a period of four months. The patient has been symptom-free without medication for three months.

CASE V. L. N., a fifty-one year old white female, had fully recovered from an attack of acute myocardial infarction in October, 1943, but developed chest pain and tightness on exertion, after meals and emotional stress in June, 1945. She had had a goiter in 1925, with nervousness

and bulging eyes, which had responded to ten months' medical treatment. In 1937, a lumbar sympathectomy was performed for hypertension.

She was a plethoric, thick-necked individual with prominent eyes but no true exophthalmos. The thyroid was not palpable. The blood pressure was 170/130, there was grade 2 retinopathy, accentuated aortic second sound, and a rough systolic murmur at the left sternal border. The x-ray showed no increase in heart size and the EKG showed left ventricular preponderance. The basal metabolic rate was minus 16, the non-protein nitrogen 33.3 mg. and the cholesterol 210 mg. per cent.

On August 4, 1945, .2 Gm. thiouracil twice daily was started. On August 27th, the basal metabolism was minus 19 per cent and the patient reported no distress or pain. The blood pressure was 140/90. The dosage was reduced to .1 Gm. three times daily and the improvement continued for the next nine weeks with the basal metabolic readings at minus 17, 16, 14, 19, 16 and 12 per cent. The blood pressure ranged between 140 and 148 systolic and 100 to 110 diastolic.

Within another four weeks, as cold weather set in, there was gradual recurrence of pain and distress and the thiouracil was gradually increased to .6 Gm. daily. The basal metabolic readings were minus 8 and minus 11 per cent and the blood pressure had returned to 170/110. After two weeks on the increased dosage, improvement occurred and the basal metabolism dropped to minus 20 per cent while the blood pressure receded to 150/80, then 130/80, and 120/80. In another four weeks the basal metabolism was minus 23 per cent, there was puffiness of the face and eyes and the patient complained of extreme sensitivity to cold. The blood cholesterol was 369 mg. per cent. Thiouracil was reduced too 0.4 Gm. daily and the puffiness gradually receded while the patient remained totally free of discomfort.

Treatment was discontinued after a total of seven months and within a week there was recurrence of all former symptoms. At this time the EKG and the chest x-ray showed no change. Propyl-thiouracil was now started but a dosage of 25 mg. three times daily for three weeks failed to control the disturbance. A greater measure

of relief followed when the dose was increased to 25 mg. five times daily but the control was not as good as that obtained with thiouracil. This level was continued for seven weeks during which the basal metabolic rate was minus 16, 10, 11, 12 and 10 per cent. It was planned to increase the dosage but the sudden death of a brother with angina precipitated a marked increase in pain necessitating hospitalization and oxygen administration for relief. EKG studies failed to reveal evidence of myocardial infarction.

Comment. This patient with severe angina and hypertension, who had formerly recovered from an acute myocardial infarction, showed improvement after three weeks of thiouracil 0.4 Gm. daily. The basal metabolic rate dropped from minus 16 to minus 19 per cent. On reducing the drug to 0.2 Gm. daily, symptoms returned and the basal metabolism rose to minus 8 and minus 11 per cent. When increased to 0.6 Gm. daily, improvement recurred and the basal metabolism dropped to minus 20 per cent, then to minus 23 per cent, when myxedema developed. On a maintenance dose of 0.4 Gm. daily the patient remained symptom-free. After seven months' treatment, thiouracil was stopped and symptoms recurred within a week. Propyl-thiouracil was substituted for ten weeks but the dosage was insufficient for control comparable to that obtained with thiouracil.

CASE VI. O. H., a forty-two-year old white male, had been having attacks of precordial pain and distress for nearly two years. These were most severe upon exertion following a meal, with the pain radiating into the throat and left shoulder and arm. Relief at first followed rest; later nitroglycerin became necessary; more recently the ineffectiveness of both these measures kept the patient from his work.

Examination disclosed an accentuated second aortic sound, a rough systolic murmur at the left sternal border and a blood pressure of 148/90. X-ray study showed no cardiac en-

largement although there was some increase in prominence of the aorta. The EKG showed left axis deviation; Q_1 and Q_2 ; depressed ST_1 with diphasic T_1 ; low voltage; positive T_2 and T_3 and absent R_3 . The precordial leads showed absent RCF_2 with elevated ST and positive T; deep QCF_4 , elevated ST and negative T; QCF_5 with depressed ST and negative T. The basal metabolic rate was plus 6 per cent.

Thiouracil, .2 Gm. three times daily, was started in August, 1945. In six days the patient developed generalized joint pain and headache which continued for four days. No thiouracil was taken for eight days then it was resumed at the lower level of .1 Gm. three times daily. No further reaction occurred.

Four weeks after beginning treatment the patient had returned to part-time work because his attacks of pain were fewer and less severe. The basal metabolism was minus 9 per cent. In another two weeks improvement was still more marked and full-time work was resumed. The basal metabolism was now minus 19 per cent. The drug was reduced to 0.1 Gm. twice daily and continued at this level for the next eight weeks, the basal metabolic readings being minus 9, 16 and 6 per cent. Coincident with the last reading there was reported a return of distress and medication was increased to 0.1 Gm. three times daily.

In the following eighteen weeks the patient was able to continue regularly at his work without notable discomfort. The basal metabolic readings during this interval were minus 13, 11, 19, 22 and 20 per cent. At this point, after eight months' continuous treatment, both lobes of the thyroid became palpable but there were no signs of myxedema. Thiouracil was discontinued but pain recurred within two days and became more marked during the next four days. Propyl-thiouracil, 25 mg. four times daily, was substituted and improvement followed after two days. This treatment was continued for twelve weeks during which there was very little discomfort and the basal metabolism was minus 23, 3 and 9 per cent. Propyl-thiouracil was discontinued and eleven months of anti-thyroid therapy terminated. The patient has continued symptom-free for one month. The EKG showed no change.

Comment. This patient with severe angina developed a drug reaction six days after starting 0.6 Gm. thiouracil daily. After a weeks' abstinence he was able to take 0.3 Gm. daily without difficulty. Improvement was noted first after four weeks and was more pronounced at the end of six weeks with corresponding basal metabolic readings of minus 9 and minus 19 per cent. Bilateral thyroid enlargement was noted after eight months' treatment. Reduction of the drug to 0.2 Gm. daily and its discontinuance allowed pain to recur. Propyl-thiouracil, 100 mg. daily, successfully controlled the disturbance for three months. After eleven months' anti-thyroid treatment the patient has remained free of angina for one month without any medication.

CASE VII. J. K., a sixty-year old white female, had hypertension for two years previous to an attack of acute posterior myocardial infarction in February, 1944. Recovery was uneventful but in September she began having occasional attacks of precordial pain following exertion and relieved by rest. Gradually these attacks became more severe and frequent in spite of continuous administration of aminophyllin and sedatives, and required six to eight tablets of nitroglycerin for their control. They would follow each meal and would come on after walking a short distance. Pain was now referred to the throat and the left shoulder and arm.

Examination showed forceful heart sounds, accentuation of the aortic second sound and a blood pressure of 140/90. The EKG showed left axis deviation with absent R in leads 3 and 4F and elevated ST with diphasic T in this latter lead. The basal metabolism was minus 6 per cent.

In September, 1945, thiouracil 0.1 Gm. three times daily, was started with little improvement during the following month. The basal metabolism was now minus 8 per cent. In another month, however, there was considerable improvement, the attacks being fewer and less severe with the need for nitroglycerin much reduced. The basal metabolism was now minus 16 per cent.

Thiouracil was discontinued at this point but within a week there was a marked increase in pain and discomfort so medication was resumed, with relief following in three to four days. She continued to improve steadily during the following three months and after a total of six months' therapy had very little discomfort and no longer needed nitroglycerin. The basal metabolic readings during this period were minus 12, 16 and 19 per cent.

Propyl-thiouracil, 25 mg. four times daily, was substituted for the thiouracil without change in the patient's condition. During the three months it was given the basal metabolism was minus 20, 19 and 17 per cent. She has been symptom-free for one month on no medication.

Comment. This patient with moderately severe angina developing several months after an attack of myocardial infarction showed improvement after two months of thiouracil, 0.3 Gm. daily. The initial basal metabolism was minus 6 per cent and at the time of improvement it was minus 16 per cent. Symptoms recurred when the thiouracil was discontinued and improved when it was resumed. Marked improvement was attained at the end of six months and this was sustained for another three months with 100 mg. daily of propyl-thiouracil substituted for the thiouracil. The patient has remained well for one month without any medication.

CASE VIII. S. D., a fifty-eight-year old white male, developed attacks of precordial tightness with radiation to the throat upon exertion five years after he had recovered from an acute anterior myocardial infarction. These increased in frequency and nine months after the onset required five to six tablets of nitroglycerin for their control.

On examination the patient was about twenty pounds overweight, the heart sounds were distant with no audible murmurs, and the blood pressure was 100/80. The EKG showed a small Q₁, negative T₃, absent R and elevated ST with upright T in CF₂ and CF₄, and a QCF₃. The basal metabolism was plus 2 per cent.

On October 9, 1945, thiouracil, .1 Gm. three times daily, was started. There was little change during the first month although the basal metabolic rate had dropped, to minus 9 per cent. At the end of another month the patient reported very little distress requiring only an occasional tablet of nitroglycerin. The basal metabolism was now minus 12 per cent. The patient failed to report for further observation.

Comment. In this instance of mild angina coming on several years after an acute myocardial infarction, there was apparent relief after two months of thiouracil, 0.3 Gm. daily. The basal metabolic rate had dropped from plus 2 to minus 12 per cent. However, the period of observation was too brief to permit classification of the result.

SUMMARY

Of eight patients with angina treated with thiouracil, five were improved, two unimproved, and one, though showing some evidence of improvement, had not been observed long enough to permit classification of the result. The two that did not respond were treated for three months and six weeks respectively. One of these, with severe angina, showed a change in the basal metabolic rate from minus 15 to minus 18 per cent. The other, with mild angina, dropped from plus 1 to minus 2 per cent. The patient with the unclassified result had a mild angina, was treated for two months, the metabolism changing from plus 2 to minus 12 per cent.

By contrast, the five who improved were treated for eight, six, seven, eight and six months, respectively, an average of seven months. Little if any improvement became manifest before two months had elapsed. The lowest basal metabolic levels reached in these patients were minus 24, 22, 23, 23 and 20 per cent.

In patients B. W. and L. B. myxedema developed at four months and five months,

respectively. Bilateral thyroid enlargement appeared in patient O. H. at the end of eight months' treatment. This constitutes valid evidence for the ability of thiouracil to suppress the normal thyroid if it is administered consistently over a long enough period of time.

Toxic reactions to the drug offered little interference in the treatment of this small group. Patient M. C. developed gastric distress at the onset which disappeared quite promptly. Patient O. H. developed joint pains and headache on the sixth day, which cleared on stopping medication for one week and did not recur on a lower dosage level.

Propyl-thiouracil, because of its lesser toxicity, was substituted for thiouracil in three patients after improvement had appeared. In patient L. B. three months' administration at 75 to 125 mg. daily failed to hold the gain made with thiouracil. One hundred mg. daily over a three months' period held the ground previously gained by patients O. H. and J. K..

Four of the five improved patients continued symptom-free without further treatment: Patient B. W. for four months, patient M. C., three months, and patients O. H. and J. K. one month each. In accounting for this and the improvement in general, it may well be claimed that a period of time alone, comparable to that devoted to treatment with thiouracil, would be sufficient to permit development of enough collateral circulation to overcome the anoxia and pain. While this might account for the ultimate improvement and freedom from attacks after treatment had been terminated, it would make no allowance for the part played by the thiouracil in lowering the metabolism, reducing the demands on the heart muscle, and in decreasing the latter's sensitivity to adrenalin. This action, though slow in developing, is apparently instrumental in controlling the symptoms in

angina while modification of existing circulatory deficiencies is being accomplished through improvement in the collateral circulation.

CONCLUSION

From the data obtained in the above study it is fair to conclude that thiouracil exerts a suppressive action on the normal

thyroid when given over a long enough period of time, and effects chemical thyroidectomy benefitting the patient with angina pectoris.

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The Effects of Quinacrine (Atabrine) Suppression on the Course of Pacific Vivax Malaria*

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THE studies reported here were designed to determine the effect of quinacrine suppression on the course of recurrent Pacific vivax malaria in a non-endemic area.

MATERIAL

Group A. Forty-nine patients were treated at this hospital for acute attacks of vivax malaria of Pacific origin with 2.8 Gm. quinacrine in seven days and were then placed on a suppressive regimen of 0.1 Gm. quinacrine daily for 150 days. Medication was administered under supervision to insure ingestion of the drug. During the period of suppression, thick malaria smears were examined weekly. Fasting plasma quinacrine levels were determined¹ every two weeks during and for one month after the period of suppression.

Group B. As a control group, sixty-nine patients were treated for acute attacks of Pacific vivax malaria with 2.8 Gm. quinacrine in seven days without subsequent suppressive medication.

Group C. Four hundred four patients who were treated for acute attacks of Pacific vivax malaria provided information on the relationship of the incidence of recurrence to the number of previous attacks. Quinacrine, chloroquine (SN 7618),^{2,3} or quinine in various dosage regimens were used in

treatment of these attacks.* The sixty-nine patients in Group B are included in this analysis. The patients are divided into five groups: (1) 116 patients who had had no previous attacks of malaria; (2) 186 patients with one to five previous attacks; (3) forty-nine patients with six to ten previous attacks; (4) forty patients with eleven to twenty previous attacks; and (5) thirteen patients with twenty-one or more previous attacks. The incidence of recurrence within 120 days in each of these groups was determined.

Following the end of antimalarial medication, whether for suppression or for treatment of an acute attack, all patients (Groups A, B, and C) were observed until the first subsequent relapse, or, if no relapse occurred, for 120 days. During this period of observation, thick malaria smears were examined once or twice weekly. No anti-malarial therapy was administered except

* The drug regimens were as follows: quinacrine, 2.8 Gm. in seven days (1.0 Gm. the first day and 0.1 Gm. three times a day for six days), 2.2 Gm. in three days (1.0 Gm. the first day and 0.6 Gm. daily for two days); chloroquine, 2.0 Gm. in seven days (0.8 Gm. the first day and 0.2 Gm. daily for six days), 1.0 Gm. in one day, 0.8 Gm. in seven days (0.2 Gm. the first day and 0.1 Gm. daily for six days), 1.5 Gm. in four days, (0.6 Gm. the first day and 0.3 Gm. daily for three days), and 1.5 Gm. in three days (0.9 Gm. the first day and 0.3 Gm. daily for two days); and quinine sulfate, 29.0 Gm. in fourteen days (3.0 Gm. the first day and 2.0 Gm. daily for thirteen days).

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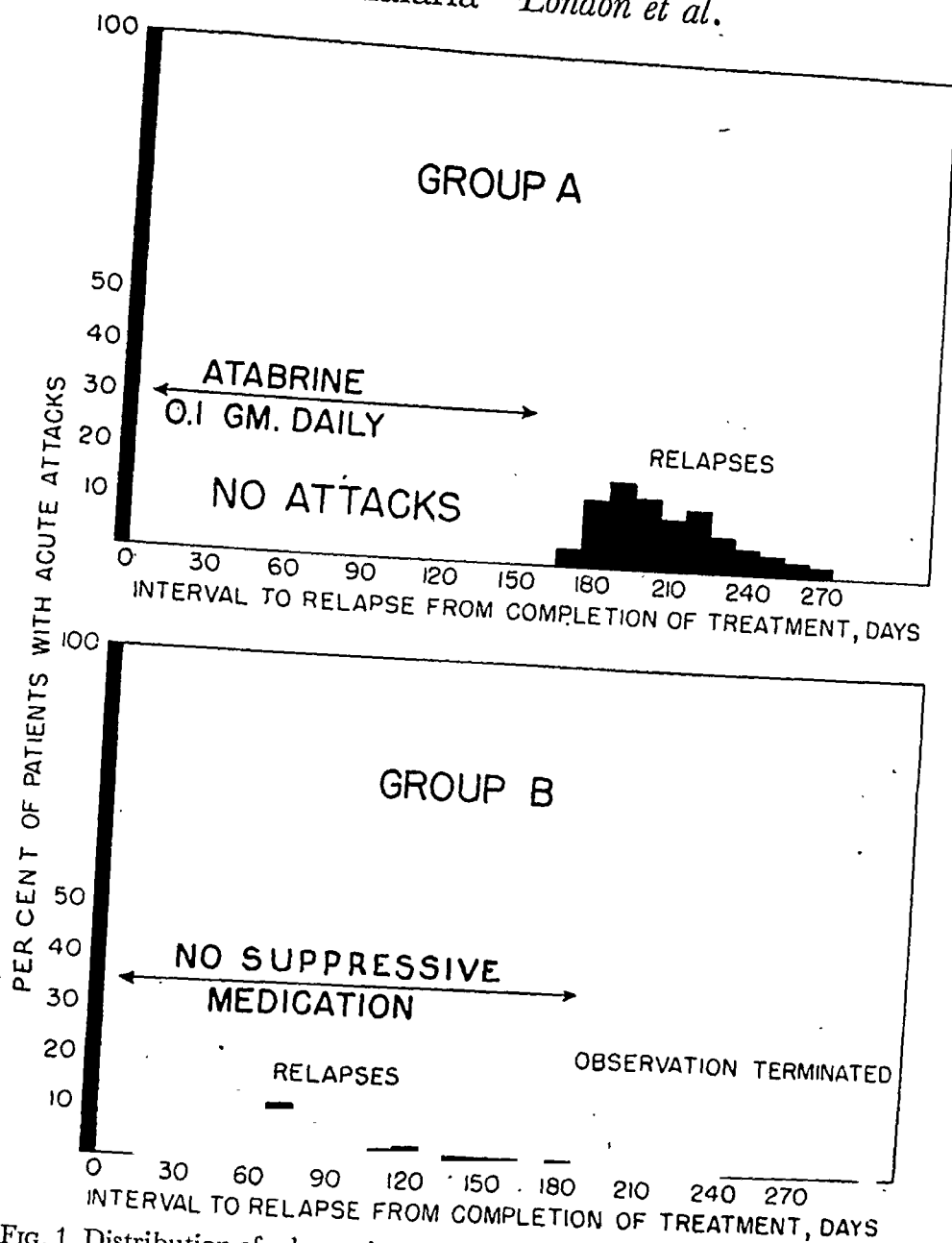


FIG. 1. Distribution of relapses in two groups of patients following treatment for acute attacks of vivax malaria of Pacific origin. Group A was placed on suppression medication 0.1 Gm. quinacrine daily for 150 days after treatment of the acute attack. Group B was treated for the acute attack but did not receive subsequent suppressive medication. Each group was observed for 120 days following the end of antimalarial medication. Note the absence of relapses in Group A during the period of suppressive medication and the similarity in the time distribution of relapses and in the rates of relapse in both groups during the 120-day observation periods.

for treatment of a clinical relapse. A patient was considered to have a clinical relapse when he had a smear positive for malaria parasites in association with an oral temperature above 100°F.

RESULTS

1. *Immediate Effect of Suppression.* During the 150 days of suppression, none of the

forty-nine patients in Group A had either asymptomatic parasitemia or a clinical relapse. The mean of the individual mean fasting plasma quinacrine levels of this group during the five months of suppression was 19 micrograms per liter.

2. *Course of Disease Following Suppression.* During the 120-day period of observation following cessation of suppressive medica-

tion, 82 per cent of the patients in Group A had a clinical relapse. This is nearly identical with the 80 per cent incidence of relapse observed in the 120 day period following treatment without suppression in control Group B. (Fig. 1.) The distribution of relapses in relation to the time following the end of suppressive or therapeutic medication is essentially the same in both groups.

Of ten patients in Group A whom we were able to observe again following treatment for the attack which terminated the first observation period, eight had another relapse within 120 days.

3. *Relationship of Incidence of Recurrence to Number of Previous Attacks.* This relationship is presented in Table I:

TABLE I
RELATIONSHIP OF NUMBER OF PREVIOUS ATTACKS TO INCIDENCE OF RECURRENCE WITHIN 120 DAYS FOLLOWING TREATMENT OF 404 ATTACKS OF PACIFIC VIVAX MALARIA

No. of Previous Attacks	No. Men Treated	Clinical Relapses within 120 Days	
		No. Men	Per Cent
0	116	81	70
1-5	186	135	73
6-10	49	38	78
11-20	40	29	73
21 or more	13	6	46

These data indicate that recurrence at a rate of 70 to 80 per cent in 120 days following treatment with quinacrine, chloroquine or quinine obtains in all groups of patients, except perhaps for a small number who have had a great many previous attacks (over twenty) and in whom the disease may "die out" more abruptly.

DISCUSSION

Our experience with large numbers of patients whom we have treated for acute attacks of Pacific vivax malaria with quinacrine, chloroquine or quinine indi-

cates that approximately 70 to 80 per cent of these patients have a recurrent attack within 120 days.^{3,4} It is reasonable to assume, therefore, that the course of the disease, in the strains of Pacific vivax malaria which we have treated, is one in which 70 to 80 per cent of patients will relapse within 120 days after treatment of an attack with quinacrine, chloroquine or quinine, and that of the patients who have relapsed, 70 to 80 per cent will have still another attack within another period of 120 days following similar treatment. It is generally accepted that vivax malaria dies out usually within two years after the last infection.⁵

Our experience with patients whom we have been able to follow through more than one attack may be cited in further support of the view that recurrence at a rate of 70 to 80 per cent within 120 days is characteristic of Pacific vivax malaria. Of 321 men treated with quinacrine, chloroquine or quinine for acute attacks, 75 per cent relapsed within 120 days. Of these, 120 men were observed again and 70 per cent of them had another attack within 120 days following the previous attack. Of this latter group, thirty-three men were followed for another period of 120 days and 70 per cent of them had a third recurrent attack under our observation.

It is recognized that this characteristic relapse rate of 70 to 80 per cent within 120 days is arbitrary inasmuch as the 120 day observation period was chosen arbitrarily. This period was chosen because it was found to be sufficiently long to include the great majority of recurrent attacks and was found at the same time to be a practical period for study of military personnel. We are aware that not all patients who relapse do so within 120 days, and, accordingly, that not all of the 20 to 30 per cent who do not relapse within 120 days represent complete cures. However, of any large group

treated with quinacrine, chloroquine or quinine, a portion of the 20 to 30 per cent, although it may be small, will have no further relapses. This is supported by the fact that the majority of any large group of patients is cured of the disease within eighteen months after the last infection.

The patients in this study were treated and admitted to the various groups as their attacks of malaria occurred, and no attempt at selection of cases was made. It is believed that this procedure minimized the influence on the rate of recurrence of factors such as differences in the severity of the original infection (i.e., the number of sporozoites introduced into the human host by the infected mosquitoes) and differences between parasite strains which may be responsible for individual variations in the frequency of relapses and in the total duration of the infection.

Our data indicate that the course of recurrence at a rate of 70 to 80 per cent in 120 days applies to patients following cessation of suppression as well as to patients who have been treated for an acute attack without subsequent suppressive medication. Of the ten patients in Group A whom we were able to observe for an additional period of 120 days following relapse, eight had recurrent attacks. Furthermore, nearly all of the malaria patients whom we treated in this hospital had received suppressive medication while overseas. As has been noted, they have followed a course of recurrence at the rate of 70 to 80 per cent within 120 days since the discontinuance of suppression.

The 82 per cent rate of recurrence within 120 days after the 150-day period of suppression demonstrates that complete suppression *per se* does not produce a diminished rate of relapse following the discontinuance of suppressive medication. These data may be interpreted as indicating that complete suppression has not shortened the course

of the disease in these patients, and, indeed, the possibility is raised that such suppression may hold the course of the disease in abeyance and thus may delay complete cure and prolong the duration of the disease in a group of patients. The exigencies of military service did not permit us to continue observation of the suppressed and unsuppressed groups throughout the course of their disease until complete cure of all patients in the groups had been achieved. Consequently, we have no conclusive demonstration that the total duration of the disease in a suppressed group is or is not prolonged.

It must be stressed that our data apply only to complete suppression for 150 days with 0.1 Gm. quinacrine daily in a non-endemic area. It is quite possible that during suppression under less well controlled conditions, the disease will continue to run its course in some patients because of mild attacks permitted by inadequate suppressive medication. Consequently, studies of incidence of attacks in such groups of men may in fact reveal a diminished relapse rate after cessation of suppression. It is conceivable that complete suppression for longer than five months might result in a diminished relapse rate after discontinuance of such suppression, and that complete suppression for as long as two years might eradicate the disease. There is as yet, however, no experimental evidence in support of such effects.

In the absence of conclusive evidence of the effect of complete suppression on the duration of the disease, the routine use of suppressive quinacrine medication for long periods in a non-endemic area seems at present inadvisable, particularly since such medication is not without danger. Serious toxic manifestations in the skin and hematopoietic system (lichen planus and eczematoid dermatitis,⁶ aplastic anemia⁷) occur in a small percentage of individuals who receive prolonged suppressive quinacrine medication. Although the toxicity of chloroquine

administered for many months is not yet clearly defined, it is known that one may encounter toxic reactions on prolonged medication.² The rational use of quinacrine or chloroquine for treatment of acute attacks, however, does not entail similar toxicity. Furthermore, when properly used, these drugs control acute attacks rapidly and permit early return to full activity. So long as the effect of prolonged suppression on the duration of the disease is not clearly delineated and prolonged suppressive regimens may produce toxicity, we believe it is preferable to treat acute attacks in unsuppressed patients rather than to use suppressive medication for long periods.

In the light of the studies and considerations which have been reported here and elsewhere,^{2,3} the following suggestions are made for the management of cases of recurrent vivax malaria of Pacific origin. Acute attacks should be treated with chloroquine or quinacrine. If a patient has had numerous debilitating attacks at frequent intervals since leaving the endemic area, it is suggested that a subsequent attack be treated with the combined quinine-plasmochin or quinine-pentaquine fourteen-day regimens. These regimens have been shown to be curative in a high percentage of cases. Indications, dosage and necessary precautions in the use of these regimens have been presented elsewhere.^{8,9}

It is further suggested that prolonged suppressive medication not be used routinely in a non-endemic area. It should be emphasized that this recommendation is not meant to apply to endemic areas, particularly in time of war when the fighting efficiency of an army exposed to malaria depends on effective suppression. In a non-endemic area, however, suppression is not advisable except in cases of intercurrent illness or in cases in which it is imperative that there be no absence from work during a limited period. Occasionally, it may also be advis-

able in prolonging the interval between recurrences in patients who are suffering from frequent attacks and who cannot spend fourteen days in the hospital as required by the quinine-plasmochin or quinine-pentaquine regimens.

SUMMARY AND CONCLUSIONS*

Quinacrine, 0.1 Gm. daily, was administered to forty-nine patients for 150 days following quinacrine treatment of an acute attack of Pacific vivax malaria. This dose was effective in suppressing completely parasitemia and clinical attacks. In a period of 120 days following termination of suppression, 82 per cent of the men had a recurrence of malaria. This incidence was the same as was found in a control group of sixty-nine men who were observed for 120 days following quinacrine treatment of the acute attack without subsequent suppressive medication. This and other evidence cited indicate that the course of the disease is not shortened by complete suppression and the possibility is raised that the duration of the disease may be prolonged. In the light of the considerations presented in these studies, routine suppression for prolonged periods in a non-endemic area is not recommended.

Recommendations for the management of Pacific vivax malaria in a non-endemic area are made.

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"Muscle Spasm" in Acute Low Back Pain and Similar Syndromes*

A New Method of Treatment with Curare (d-Tubocurarine in Oil and Wax)

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THE entity clinically designated as "muscle spasm" is an integral part of many of the common wear and tear syndromes of every day practice. The term is loosely used but roughly may be defined as a state of transient muscle contraction, not amenable to voluntary control, characterized by resistance to stretch and usually associated with pain on attempted extension.

Clinically, the picture is well recognized. It may be a muscle response to irritation, whether inflammatory or traumatic. It may be reflex in origin and secondary to pathological conditions, visceral or somatic, of like segmental neural connection. Kellgren,¹ Wolff² and others have shown that this latter type of muscle spasm may be perpetuated after cessation of the initiating stimulus and thus present a major treatment problem.

The various lesions which together make up the low back syndrome are excellent examples of the importance of the problem of muscle spasm in treatment. The initiating trauma or etiologic agent is followed by muscle splinting as a protective measure. Pain enhances the splinting or spasm, which in turn is followed by more severe pain and further muscle spasm. The vicious cycle is self-perpetuating. Whether the intense pain is at least partly ischemic in origin is not fully understood.

Dramatic relief may be afforded by any agent which tends to interrupt and break up the cycle of splinting and pain. There are many traditional measures, all of which have some rationale and serve their purpose, at times, admirably. These include heat, traction, ethyl chloride spray, novocaine or saline injections, and heavy sedation. Unfortunately, none of these measures is specific or generally reliable in a series of cases.

Since curare is known to create a myoneural block, it is logical to try to apply its properties to the treatment of muscle spasm. Unfortunately, in aqueous solution its action is evanescent, with poor control of blood levels, and its therapeutic margin is narrow, particularly in the ambulatory or casually observed patient. A newer preparation, tubocurarine in oil and wax,[†] previously described by one of the authors,^{3,4,5} circumvents to a great extent these therapeutic limitations by providing slow absorption at fairly predictable levels of saturation. In previous reports, it has been shown that with this preparation it is possible to create a partial block at the myoneural junction without loss of voluntary function or any unpleasant curare side effects.

The series of cases presented in this paper has been treated with the aforementioned

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TABLE I

ACUTE LOW BACK DISORDERS OR SIMILAR SYNDROMES

I. Associated with structural abnormalities, such as osteoarthritis and congenital or acquired deformities.

Name	Diagnosis	Symptoms and Signs	Previous Treatment	Response to Curare	Reaction
H. H.	Acute low back strain, sacralisation L ₅ with osteoarthritis	Severe low back pain Marked splinting Loss normal lordosis	Traction Heat Morphia	Complete relief of diffuse severe pain with muscle relaxation in 2 hrs. Pain now localized to L ₅ body on movement only	None
L. T.	Kyphosis and scoliosis upper thoracic spine	Constant pain and aching with muscle spasm T ₁ region and spinatus group	Massage	Relief of pain and aching discomfort	Diplopia 1½ hrs.
H. S.	Osteo arthritis spine with acute low back strain	Severe generalized low back pain with immobility, some sciatic radiation	Diathermy Static wave	Relief of severe pain Residual soreness Loss sciatic pain	Dizziness 2 hrs.
C. D.	Unstable back with sacralisation L ₅ , acute low back strain	Loss lordosis Immobility of back Severe generalized pain	Ethyl chloride Heat	Subsidence of generalized pain, residual aching in sacral region	Diplopia 1 hr.
L. R.	Lumbosacral osteoarthritis with scoliosis. Degenerative disease of the intervertebral disc with narrowing	Weak back for years Severe low back pain 2 months with occasional radiation to rt. leg	Heat	Relief of severe pain in 2 hrs. Slight soreness low back	Drowsy next day
E. Y.	Osteoarthritis cervical spine with cervical 'myositis'	Splinting trapezii, erector capiteae Lack of mobility of head and shoulders	Heat Massage	Relief of pain Marked increase in mobility. Residual soreness	None
L. M.	Infarct vertebral body L ₄ (sickle cell)	Splinting lumbosacral muscles with immobility and severe pain	Heat Bedboards	Reduction of spasm, able to move about, pain localized to site of pathology	None
H. S.	Acute low back strain, osteoarthritic changes with degenerative disc disease and narrowing of lumbar interspaces	Severe generalized pain with marked lumbosacral tilt, immobility of lumbar spine	Heat Corset Massage	Relief of generalized pain, increased mobility	Diplopia 1 hr.
E. S.	Osteoarthritis cervical spine with spurs	Severe neck and shoulder girdle pain, limitation of movement, headache	Diathermy Massage	Relief of constant pain and headache in 2 hrs. Residual soreness, increased mobility	None

II. With no demonstrable structural abnormalities.

K. K.	Acute low back syndrome	Severe lumbosacral pain with tilt to right Loss of lordosis, left sciatic pain, immobility	Heat Morphia	Dramatic relief in 3 hrs. of sciatic and low back pain Residual soreness	None
H. B.	Autonomic disturbance with trapezius, erector capiteae and shoulder girdle muscle spasm	Severe neck and shoulder pain radiating down arms. Immobility of neck	Morphia Heat Massage	Marked relief, residual soreness	None

TABLE I (Continued)

Name	Diagnosis	Symptoms and Signs	Previous Treatment	Response to Curare	Reaction
III. Following operation for removal of herniation of nucleus pulposus.					
H. B.	Post-op. herniated nucleus pulposus with low back syndrome, recurrent, and pyelitis C	Severe erector spinae spasm with complete immobility of low back and generalized pain	Heat Morphia Massage	Increase in mobility Loss of excruciating pain, residualsorenessmarked	None
H. H.	Post-op. laminectomy for herniated nucleus pulposus	Excruciating generalized low back pain; immobility of spine, loss lordosis	Corset Heat Novocaine Morphia	Dramatic complete relief in 2 hrs. Able to move about freely, soreness in muscles of low back	None
J. G.	Post-op. herniated nucleus pulposus Recurrent pain and muscle spasm of glutei and paravertebral muscles	Immobility, generalized low back pain	Heat Bedboards Massage	Relief generalized pain, increased mobility, 'pain now in bones'	Diplopia few minutes
IV. Associated with nerve root compression.					
D. W.	Herniated nucleus pulposus narrowing of interspace	Low back pain, ? sciatic radiation, and abdominal distention	Morphia Traction Bedboards	No relief, accentuation segmental distribution of sciatic pain	None

curare suspension, usually after conventional methods have failed. It has been consistently possible to break up muscle spasm and enhance recovery rate when the initiating pathological condition is static or brought under control. Where the pain and local muscle spasm were secondary to a continuing stimulus, i.e., root compression, radicular pain persisted after reduction of the spasm and the local or reflex spasm often recurred shortly. This response may prove to be a useful diagnostic test and will be discussed later in the paper.

The cases studied run the gamut of low back disorders, including the usual orthopedic disturbances, so-called low back strain, osteoarthritis of the spine, actual vertebral lesions, disc lesions and also some instances showing reflex spasm secondary to remote disease. Table I is a compilation of typical cases and results.

It is apparent from a perusal of the above data that in many cases of low back syn-

drome an abrupt cessation of the major complaints often follows upon relief of muscle spasm. The sequence of events after treatment is of interest. The patient usually notes an abrupt relief of major pain within several hours after injection. Mobility is increased and the patient often describes a feeling of pleasurable relaxation, even drowsiness. The severe pain is followed by muscle soreness and localized pain in the region of actual disease, if it is capable of local signature. The soreness is a logical sequel, since protracted muscle contraction is associated with diminished vascular exchange and ischemia. It is known that, depending upon the chronicity of the process, the muscle involved may thus show reversible inflammatory changes, cloudy swelling, etc. The characteristic tenderness which remains even after complete relief of pain seems to have its basis in this transient pathologic state.

Three case histories are described in detail since they are representative of the general results:

CASE REPORTS

CASE I. H. H., a forty-eight-year old male, member of a medical college faculty, over a period of years has had occasional lumbosacral pain with moderate muscle spasm. These attacks were self-limited and disappeared without residue. In recent years, the patient had grown much heavier and had led a more sedentary existence. In February, 1946, he began to note recurrence of lumbosacral pain. This became increasingly severe over a period of days and he was admitted to the hospital. On mild sedation, bed boards and rather haphazard traction, he improved enough in three days to be discharged. X-ray examination had revealed an unstable lumbosacral joint with proliferative arthritis in the joint region.

Two days later pain had increased to its former severity and the patient was again hospitalized. Muscle spasm at this time was more pronounced, and the patient was in constant severe discomfort in all positions. Traction was reinstituted without relief. Morphia and sedation were used in large doses. The orthopedic consultant advised a body spica, full length, and this was applied. The patient complained more and more bitterly, remained sleepless and unrelieved by any form of medication. At the end of four days, spinal anesthesia was contemplated in a heroic attempt to reduce the marked muscle spasm of the entire low back region with the accompanying severe pain. A trial of curare in oil was agreed upon instead. One cc. of the suspension was given in the right buttock. Two hours later, the patient stated that his back muscles had relaxed and at the same time the accompanying generalized pain had vanished. The reduction in muscle spasm was immediately demonstrable on examination. The patient now noted only focal pain on motion at the lumbosacral articulation. Relief of pain was followed by adequate rest without medication. The patient became less tense, began to eat and regain his normal equilibrium. However, by the third day, in dread of a recurrence, he

requested a second injection. The same dose of drug was given at this time and again three days later. The spasm never recurred and the patient's subsequent convalescence was completely uneventful. A back brace was prescribed by the orthopedist and when this was fitted, the patient was allowed up and discharged from the hospital.

CASE II. K. K., a fifty-year old woman, was admitted as an emergency because of excruciating low back pain with left sciatic radiation. She was unable to move about without evoking showers of pain throughout the lumbosacral region and down the left leg. She lay in bed with the low back characteristically immobile, and the left leg supported on pillows at the knee. Examination was impossible because of the extreme pain and x-ray examination could not be carried out. Conventional medication afforded minimal relief. One cc. of *d*-tubocurarine in oil was injected in the left gluteal region and in two hours the patient had noted an almost complete cessation of pain. She was able to move about and physical examination and x-rays were performed. There was no evidence of nerve root compression on examination. X-rays showed normal low back structures but an arthritic process about the hip joint. As the pain and muscle spasm of the low back diminished, the sciatic reference of pain gradually disappeared. Within three days, the patient was up and about her room and shortly was discharged free of symptoms.

CASE III. D. W., a fifty-four year old male, had had recurrent attacks of low back pain since he lifted a heavy weight some time ago. On admission, he complained of severe lumbosacral pain with radiation to the right knee. When standing, his posture was stooped, with the low back immobile and the right leg flexed protectively at the knee. There was marked splinting of the erector spinae muscle group. On traction, heat and bed boards, he developed abdominal distention of such degree that intubation was necessary. Prostigmin and pitresin afforded no relief. In the hope that curare might reduce his low back signs and therefore ameliorate the reflex distention, he was given 0.9 cc. of *d*-tubocurarine in oil and wax, intramuscularly. Coincidentally, and with vigorous treatment, the distention was relieved.

After curare, the patient noted definite sciatic distribution of pain on coughing and sneezing and the segmental nature of his leg pain became objectively more evident. At operation, subsequently, a large protruded herniation of the nucleus pulposus was found at the fourth lumbar interspace on the right.

These cases are cited to delineate the value of the response to curare therapy as a diagnostic test. As described above, relief of muscle spasm ordinarily is followed by abrupt relief of local pain and its reference. However, where root compression, such as in herniation of the nucleus pulposus, is the exciting and continuing stimulus, the relief of local muscle spasm does not influence the severe pain and actually may highlight its segmental nature by removing temporarily the purposeful splinting action of the muscle spasm.

Several cases are included in Table I in which the pathological process is very similar but of different anatomical distribution. Where the same criteria are met, the results are much the same. However, it should be stressed that muscle spasm of the erector capiti and trapezius groups is more difficult to treat, since these muscles are seldom out of use and unless specifically prescribed, are difficult to put at rest. Strict bed rest is of major importance to successful therapy.

Among all the pathological entities which may be classified as "wear and tear" syndromes, rheumatoid arthritis seems the most refractory to treatment. There are few, if any, specific therapeutic measures. It has seemed worth while to evaluate the effect of curare in the acute phase of the disease, since to the clinician at this stage there are changes similar to skeletal muscle spasm. The authors are fully aware of the danger involved in the indiscriminate use of the term "muscle spasm." So far as the aforementioned conditions are concerned, the entity is clear-cut. In rheumatoid arth-

ritis there is a very similar clinical picture, arising perhaps out of different mechanisms. Several factors are at play. In addition to joint inflammation, there may be infiltration of the actual muscle mass by inflammatory exudate. Freund et al.⁶ have described lymphorrhagic infiltrations in the peripheral nerves. All these irritative phenomena apparently either directly or reflexly give rise to the extreme pain on attempted stretch or attainment of full range of motion.

The typical protective position adopted in an attempt to prevent pain is a major cause of deformity, reversible early but static in the later stages of the process. Long periods of fixation, with unwillingness to perform normal movements because of intense pain, lead to atrophy of disuse and fibrosis.

The clinical goal is, first the prevention of long standing protective splinting with subsequent muscle changes and disturbances of joint function, and secondly, the alleviation of pain. In early cases, it has been routinely possible to influence favorably the characteristic flexion deformity during the period of treatment. Pain in these cases is based upon a complex combination of factors, but with relief of abnormal muscle tension there seemed to be a gratifying diminution in pain. Major forms of analgesia could be discontinued and the residual pain controlled well with traditional medication such as aspirin.

The following case reports illustrate the type of disorder amenable to treatment and the therapeutic results obtained.

CASE IV. E. S., a twenty-five-year old woman, suffered with severe rheumatoid arthritis for six months. On admission her sedimentation rate was markedly elevated and agglutination with hemolytic streptococcus group A was positive. Flexion contracture of both elbows was present with extension possible only to 110 degrees, with severe pain supervening beyond this range. Her fingers were characteris-

tically fusiform. The patient was admitted to the hospital partially curarized over a period of four days with 1 to 1.1 cc. of *d*-tubocurarine in oil and wax daily. After saturation with drug, her elbows could be extended completely without pain. She was given two transfusions with whole blood, gold therapy was started, and she was discharged to the clinic where curare was continued twice weekly and later weekly. Exercise was encouraged. At the present time she is free of pain, has complete extension of elbows and knees and sleeps soundly. She is ambulatory, carries out her housework and drives a car. Of interest is the fact that she has very little atrophy of the small muscles of the hand at present. During the course of treatment she noted slight drowsiness on several occasions and diplopia momentarily on one occasion.

CASE V. D. D., a male of thirty, had had an acute onset of peripheral joint and back pain two months before admission. One year and again four months previously, he had been treated successfully for gonorrheal urethritis. At another hospital massive quantities of penicillin had been injected intramuscularly and into a knee joint without benefit to his present complaints. On admission he was in marked distress with flexion contractures of both elbows to 85 degrees and of both knees to 100 degrees. These could be overcome passively only very slowly and with much pain to the patient. Spine x-rays showed changes in three of the apophyseal joints of the lumbar spine and in the right sacroiliac joint. Examination of the peripheral joints showed no heat, redness or swelling, and x-rays were negative. The patient ran a fever of 101°F. daily and for four days was treated with analgesics. Pain remained severe and sleep was very poor on 200 to 250 mg. of demerol daily. He was started on 1 cc. of *d*-tubocurarine in oil and wax daily and by the third day pain could be well controlled with aspirin and codeine. He was able to extend his arms and legs actively. Partial curarization was maintained and he was started on x-ray therapy, on which treatment he showed a marked exacerbation of symptoms. During curare treatment, the patient noted double vision on one occasion for about thirty minutes, but no other side effects were encountered.

In recognition of the difficulty in assaying therapeutic results in rheumatoid arthritis, the apparent beneficial effect of curare must be interpreted with caution. However, results are sufficiently encouraging to warrant extension of the present study. An attempt is being made to support clinical impressions by objective measurements. It is hoped that a larger body of cases with objective correlative data can be reported at a later date.

SUMMARY

In an attempt to exploit the physiological properties of curare in the treatment of muscle spasm, a new preparation has been used. This preparation, *d*-tubocurarine in oil and wax, because of its slow absorption affords a much more satisfactory therapeutic index and a more prolonged effect than the aqueous solution. A series of cases in which patients with true muscle spasm were treated is described, and in addition a small group with a similar clinical picture but of possibly different origin is included.

CONCLUSIONS

1. "Muscle spasm" is often an integral part of the clinical picture of the acute low back syndrome.
2. Striking relief of symptoms in "low back" and similar syndromes may follow alleviation of muscle spasm.
3. A suspension of *d*-tubocurarine in oil and wax has proven very useful in breaking up the muscle spasm present in the conditions.
4. The difference in the response of patients exhibiting root compression from those with other types of disorders is described, and is suggested as a diagnostic test.
5. The use of *d*-tubocurarine in oil and wax for the prevention of deformity and alleviation of pain in early rheumatoid arthritis has led to promising results in a small group of patients.

6. On the basis of the clinical results so far obtained, it is believed that further exploration of this form of therapy is warranted.

The authors wish to express their obligation to the Attending Staff of the Columbia-Presbyterian Medical Center for the opportunity to study many of the cases presented in this series, and, in particular, to the late Dr. Clement B. Masson, whose unflagging interest and cooperation had much to do with making this work possible.

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Subacute Bacterial (Streptococcus Viridans) Endocarditis Treated with Penicillin*

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IT has been only about three years since a patient with subacute bacterial endocarditis was an unfortunate object who had no hope, served no purpose other than to contribute his physical signs to the teaching of physical diagnosis, and finally his viscera to the study of gross and microscopic pathology. However, in this brief interim the use of penicillin has provided interest, animation, and, indeed, life itself to the majority of these individuals. There have been reports of a number of cures. Chief among these are the series of Dawson and Hunter,^{1a} Loewe,² Loewe, Rosenblatt, Greene and Russell,³ Bloomfield and Halpern,⁴ Meads, Harris and Finland⁵ and Bloomfield, Armstrong and Kirby.⁶ Many other isolated cases and small groups of cases have also been recorded. Although the disease is not rare, it does not occur commonly enough to produce series involving large numbers of cases. Thus conclusions must be drawn from smaller multiple series, and it is therefore important that many reported series be carefully studied not only from the standpoint of the cures effected but also from the standpoint of failures encountered.

As in all diseases, early diagnosis and treatment are of paramount importance. Noteworthy in these and other published data is the unduly long period of time elapsing between the onset of symptoms, diagnosis and treatment. This period averaged fourteen and one-half weeks in this

series. In spite of the high recovery rate, however, the occurrence and persistence of cardiac insufficiency following the infection and recovery gives the impression that this complication might have been obviated by earlier diagnosis and treatment. A presumptive diagnosis of subacute bacterial endocarditis should always be made in any patient having a heart murmur in conjunction with any one of the following: Chills, fever, emboli, splenomegaly, clubbed nails, hematuria or repeated pains in the back. A positive diagnosis may be made with a combination of the above plus the finding of *Streptococcus viridans* upon repeated blood cultures. Blood cultures should be taken twice or three times each day over a period of three or four days. This is important because it has been noted that positive cultures may be obtained either when the temperature is low or high. Cultures should be planted in blood agar plates and liquid media both aerobically and anaerobically, since different strains of *Streptococcus viridans* may be aerobes, anaerobes or facultative anaerobes. It is of exceptional interest to note that one of this series (no. 35749) was referred because of rheumatic heart disease with congestive heart failure, and although he at no time had any fever or leukocytosis, was found to have an enlarged spleen. This in conjunction with the heart murmur satisfied the requirements for a presumptive diagnosis of bacterial endocarditis. In all, nine blood cultures were

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nade during three successive days. All were sterile except numbers 3, 5 and 9. These cultures showed from eleven to twenty-two colonies of *Streptococcus viridans* per cc. of blood. Obtaining blood cultures in this manner obviously will save time and add to the accuracy of the diagnosis. Early recognition and treatment might possibly obviate the occurrence of a fatal or crippling cerebral or other embolus and might indeed mean the difference between the success or failure of treatment.

This group of patients exhibited a clinical feature which has been outstanding in almost all patients with subacute bacterial (*Streptococcus viridans*) endocarditis which I have observed. In practically every instance these patients are perfectly willing to undergo any hardship in order to recover. I have never observed a patient with this disease who has not cooperated cheerfully and accepted any proposed treatment, from multiple needle punctures to artificial fever. This characteristic seems to be as typical in this disease as embolic phenomena or any of the other clinical or laboratory aspects. Bacterial endocarditis has not been proven where lack of cooperation, psychoneurotic tendencies and unwarranted complaining have been present in a suspected patient.

As yet there is little conclusive data as to the exact manner in which the lesions heal. Since there is practically no blood supply in the diseased valves, other than those involved by syphilis,⁷ it seems only logical that the constant bathing of the vegetations by penicillin brings about healing by gradual penetration from the surface of the lesions. This would explain the necessity for prolongation of treatment until the vegetations have healed to their bases. The pathological findings in two patients who had healed subacute bacterial endocarditis lesions were reported by Rosenblatt and Loewe.⁸ Healing with endothelialization of the diseased valves was noted. These

patients died as the result of congestive cardiac failure several months after treatment. Cultures of the valves and adjacent myocardium were found sterile.

Congestive heart failure was a prominent cause of death in the majority of reports setting forth the mode of death, both before and since the advent of penicillin. It occurred in eight instances or 67 per cent of this series. In the eight of the eleven patients cured of their lesions but who died with congestive heart failure, seven or 88 per cent showed marked improvement from the standpoint of cardiac insufficiency after treatment with penicillin. Therefore, these findings indicate that one is not justified in presuming the ultimate disability to be so great as to warrant depriving any individual of treatment. Early and vigorous management of cardiac failure has probably contributed to the success of this series.

In vitro studies are important. It has been shown by Ellard Yow and his associates¹⁰ that these laboratory procedures are a reliable guide in determining the type of antibiotic which is best suited for the bacterium involved. Unfortunately, some strains of *Streptococcus viridans* are not inhibited by penicillin, even in high concentration. In this series all strains of *Streptococcus viridans* were found to be sensitive to penicillin in a dilution of 1 unit per cc. These authors point out that blood levels higher than 0.1 unit per cc. are but very rarely obtainable. Subsequent *in vitro* studies have been conducted with penicillin dilutions of 1.0, 0.1 and 0.05 unit per cc. These more nearly approximate expected blood levels in patients.

From Table 1 it is learned that the total dosage of penicillin varied greatly, especially in those treated early in the series at which time there was no standard procedure, penicillin was available only in very limited quantities, and the dosage was often quite small. Indeed, there is no fixed

TABLE I
SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS *

Case Number...	25818	31234	35749	34932	City Hosp.	38396	39286	39748	38514	39242	43933	36529
Age.....	40	9	30	22	68	42	4	51	21	4	24	28
Sex.....	Male	Male	Male	Female	Female	Male	Female	Male	Female	Male	Female	Female
Basic lesion.....	Rheumatic mitral stenosis	Patent inter-ventricular septum	Rheumatic mitral stenosis, aortic regurgitation	Mitral stenosis, rheumatic	Rheumatic mitral and aortic regurgitation	Rheumatic mitral stenosis, aortic regurgitation	Patent inter-ventricular septum	Aortic stenosis, mitral stenosis, rheumatic	Patent ductus arteriosus	Patent ductus arteriosus and other congenital defects	Patent ductus arteriosus	Aortic insufficiency, mitral stenosis, rheumatic
Duration of illness before treatment.	7 weeks	4 months	Not known, no symptoms, palpable spleen only	4 weeks	5 weeks	5 months	2 months	7 months	6 months	6 weeks	4 months	3½ months
Injecting bacterium.	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans
Complications..	None	Cardiac infarct, cardiac insufficiency	Cardiac insufficiency	Cardiac insufficiency	Cardiac insufficiency	Cardiac insufficiency	None	Duodenal ulcer, cardiac insufficiency	Pulmonary infarctions, mild cardiac insufficiency	Cardiac insufficiency, pericardial effusion	Pulmonary infarctions, mild cardiac, insufficiency	Congestive failure, ruptured aortic aneurysms
Embolic phenomena.	Generalized small	Lungs, spleen and generalized	Spleen, kidneys, finger tips	Multiple peptic ulcers in skin	None	Spleen, kidneys, generalized	None	Spleen, kidneys, insufficiency	Spleen, kidneys, fingers	Kidneys, spleen, generalized	Lungs, spleen, kidneys, generalized	Multiple at onset none after cultures negative and temp. normal
In vitro studies...	Inhibited by penicillin not by sulfonamides	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Cultures obtained elsewhere	Inhibited by penicillin	Cultures obtained elsewhere	Inhibited by penicillin at outset, but later only in concentration greater than 1 u. per cc.	Inhibited by penicillin	Inhibited by penicillin
Treatment.....	Penicillin 5,000,000 units 21 days, I.M.	Penicillin (a) 2,030,000 units 20 days, (b) 2,000,000 units 20 days, I.M. drip	Penicillin 3,150,000 units 14 days, I.M.	Penicillin 3,335,000 units 21 days, I.M.	Penicillin 5,200,000 units 22 days	Penicillin 4,000,000 units 20 days I.M.	Penicillin 4,885,000 units 42 days, I.M.	Penicillin 3,520,000 units 15 days, I.M.	Penicillin (a) 400,000 units 4 days, (b) 600,000 units 6 days, (c) 1,000,000 units 10 days, (d) 2,000,000 units 20 days, (e) 4,200,000 units 21 days, Total 8,200,000 units 61 days	Penicillin 6,980,000 units 43 days, Para-amino-hippuric acid 8 days	Penicillin (a) 600,000 units 6 days, (b) 2,000,000 units 20 days, (c) 2,000,000 units 20 days, (d) 5,000,000 units 21 days, Total 9,600,000 units 67 days	Penicillin 6,250,000 units 25 days
Sequelae.....	None	None	None	None	None	None	None	Subdeltoid abscess	Excision of ductus arteriosus	Congestive heart failure	Excision of ductus arteriosus	Cardiac failure bacterial lesions healed
Blood cultures sterile.....	24 hours	24 hours	12 hours	4 days	12 hours	12 hours	24 hours	12 hours	24 hours	42 days	24 hours	24 hours
Cause of death..
Result follow-up.	Cure 24 months	Cure—no cardiac insufficiency 22 months	Cure—slight cardiac insufficiency 19 months	Cure 19 months	Cure—cardiac failure markedly improved. 17 months	Cure—no cardiac insufficiency. 16 months	Cure 15 months	Cure 15 months	Cure 14 months	Cured—definite failure, cultures sterile. 13 months	Cure—murmurs and third conc. 12 months	Cardiac failure bacterial lesions healed Died—10 weeks after cultures sterile

* Her application of twelve cases of subacute bacterial (Streptococcus viridans) endocarditis.



FIG. 1. The margins of the aortic cusps are rolled and thickened. The surfaces are glistening and free of vegetations or other active inflammatory changes. Probes are in place through the four perforations of the valve cusps. These perforations resulted from mycotic aneurysm formation. Marked hypertrophy and dilatation of the left ventricle are evident.

standard procedure today. There seems to be general agreement, nevertheless, that a minimum treatment period of six to eight weeks, employing a daily dosage of 250,000 units of penicillin is desirable. When one considers the deep seated implantation of the bacteria in the vegetations, the advisability of prolonged treatment becomes obvious. The failure of sulfonamides and other bacteriostatic agents to penetrate these lesions in many cases probably has accounted for their failure in most instances. Meads⁹ has pointed out the urgency of giving adequate dosages of penicillin in any type of infection which might be susceptible to this agent. Therefore, the total daily dosage should be increased in the event of continued positive blood cultures or fever, and the time interval shortened as the case demands.

Other matters of importance are blood transfusions, adequate nutrition, general hygienic care, and, when practicable, the elimination of focal *Streptococcus viridans* infection. This type of infection has been

found principally about the teeth and gums, and is best managed while the patient is still maintained on a full blood concentration of penicillin. If gingivitis of appreciable degree exists along with dental caries, extensive dental extractions should be performed. This has resulted in negative blood cultures in one patient who previously had exhibited occasional positive cultures during the course of her therapy.

The following series (Table 1) embraces twelve cases of proven subacute (*Streptococcus viridans*) endocarditis treated with penicillin. All have been followed for from twelve to twenty-four months. Of these eleven (or 92 per cent) are still alive and well. A number of patients have been treated since but have not been observed over a sufficient period of time to warrant reporting at this time. Heparin or other anticoagulants were not employed in any of these cases.

One patient (34932) developed a recurrence of her *Streptococcus viridans* infection and the classical picture of subacute

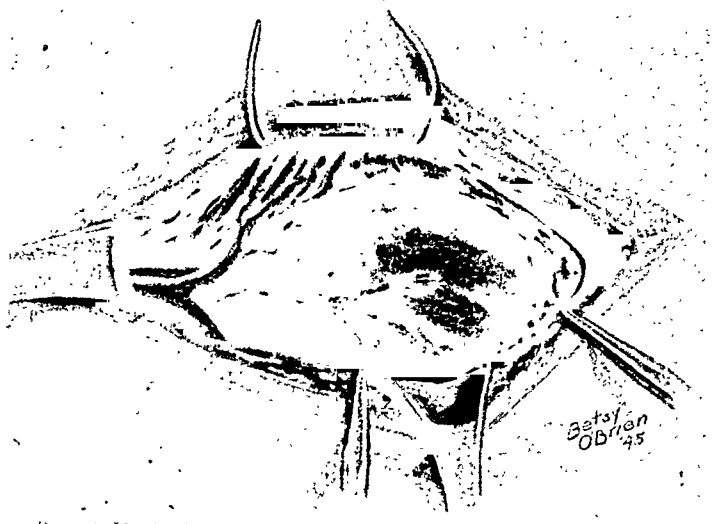


FIG. 2. Drawing at operation of the mycotic aneurysm of the right popliteal artery.

bacterial endocarditis with multiple emboli. The organisms recovered in blood cultures were found to be sensitive to penicillin *in vitro*, and penicillin therapy resulted rapidly in a good clinical response and negative blood cultures. She was free of fever and clinically well three months after treatment of the second infection.

An autopsy was performed on one of the twelve who expired (36529) and death was found to be due to congestive cardiac failure and pneumonitis. At the time of her original admission she showed frank evidence of perforation of the aortic valve in the form of a grade v or vi "base violin string type" of diastolic murmur along the entire sternum and an accompanying pronounced diastolic thrill. As noted in Table I, the cultures were free of *Streptococcus viridans* within twenty-four hours after penicillin was instituted, and they remained so for ten weeks. Furthermore, the sedimentation rate was normal. The added factor of cardiac failure brought about by left ventricular strain as the result of the multiple perforations in the aortic cusps was the most direct cause of death. Pathologic findings showed chronic mitral and aortic rheumatic valvular disease with no evidences of remaining *Streptococcus viridans* infection. The perforations in the

aortic valve are illustrated in Figure 1. A further interesting complication was a mycotic aneurysm of the right popliteal artery, which was excised after penicillin therapy was started. (Fig. 2.)

DISCUSSION

Twelve patients with subacute bacterial (*Streptococcus viridans*) endocarditis which have been treated with penicillin are presented. Eleven (or 92 per cent) are alive and well from twelve to twenty-four months after treatment. Pertinent data are summarized in Table I. Anticoagulants were not employed.

The success of the treatment of subacute bacterial endocarditis lies first in early diagnosis, which is hastened and confirmed by obtaining blood cultures three times daily for three successive days; second, in prolonged treatment with penicillin in adequate dosage; third, management of the cardiac failure; fourth, employment of general measures, especially blood transfusions and replacement of serum proteins; and fifth, in the use of *in vitro* studies which are of inestimable value in prognosis and in governing the course of therapy.

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Folic Acid and the Bone Marrow in Radiation Therapy*

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FROM October, 1942, to July, 1946, 191 cases of lymphoblastomas were observed. This group included giant follicular lymphoblastoma, lymphosarcoma, reticulum cell sarcoma and Hodgkin's disease. The bone marrow studies revealed in all instances a marked depression of the myelopoietic and erythropoietic systems. The normal myeloid-erythroid ratio varied between 2:1 and 8:1 and the myeloid-lymphoid ratio 5:1. It was noted that the decrease in the myeloid-erythroid elements was of a depressed type with the ratios more or less constantly maintained, whereas the myeloid-lymphoid ratios were almost completely reversed, i.e., 0.5:5. These features were observed consistently when the bone marrow was studied on admission. It was assumed that these effects were due primarily to the overactivity of the reticulo-endothelial system in these diseases. These bone marrow effects were reflected in the peripheral blood by a marked anemia and neutropenia with an increase in the lymphocytic elements. In the lymphoblastomas this cytophagic and hormonal (?) depressant effect on the bone marrow would seem to be rather comparable to the depressant effects seen on these structures in primary splenic neutropenia, thrombocytopenia, splenic pancytopenia and Felty's syndrome.

When radiation therapy was introduced in the treatment, the anemia and neutropenia became progressively more severe necessitating on the average daily to weekly transfusions of red cells or whole blood in

order to maintain, as closely as possible, the red cell, hemoglobin and neutrophilic levels within normal limits. These depressant and destructive effects on the bone marrow elements are believed to be due to a combination of the excessive cytophagic activity of the reticulo-endothelial system in these diseases and the destructive effects of radiation.

There were 122 cases given routine radiation therapy accompanied by transfusions. In all of these cases the average length of hospitalization was nine and eight-tenths months with a range from five to thirteen months. The radiation reactions and the general depressant effects were severe. The bone marrow and peripheral blood remained continually abnormal. The sedimentation rates decreased slowly but never returned to normal. The stress on blood bank, donors, laboratory and hospital personnel consequent to maintaining a semblance of hematologic equilibrium in these patients during radiation therapy was profound. These factors were so formidable that an adjunct to this therapy was sought. Beginning January, 1944, the Lederle Laboratories, through the courtesy of Doctor Thomas Jukes, supplied liberal quantities of folic acid. This was supplied in bulk powder and in capsule form so that large dosages could be given routinely ranging from 75 to 150 mg. three times daily. Considerable counsel and aid was given by Dr. Daft and Dr. Sebrell of the National Institute of Health, Washington, D. C.

* From the Department of Medicine, Woman's Medical College, Phila., Pa.

There were seventeen patients treated with large doses of folic acid without any other therapy. There was no demonstrable beneficial influence on the course of the disease. Subsequently these cases were given radiation therapy.

There were sixty-nine patients treated with radiation therapy, transfusions and folic acid. When folic acid was added to radiation therapy, it was noted that the patients withstood radiation therapy better, with less nausea, vomiting and general depressing physical effects. The sedimentation rates returned less slowly to normal. The necessity for red cell or whole blood transfusions decreased in frequency to an average of one in eighteen days. The average time of hospitalization was reduced from nine and eight-tenths months to five and three-tenths months with a range from three to six months. The bone marrow on discharge showed an increase in the myeloid and erythroid elements and the myeloid-lymphoid ratios tended to return to normal although they never reached normal.

SUMMARY

There were 122 patients with lymphoblastoma treated with radiation therapy and transfusions. The depressant effect on the bone marrow by the disease and therapy was profound.

Seventeen patients were treated with folic acid alone without any demonstrable effect on the course of the disease.

Sixty-nine patients were treated with folic acid in addition to routine therapy. The addition of folic acid seemed to decrease the deleterious and depressant effects of radiation therapy on the bone marrow, decrease the necessity for as frequent transfusions, shorten the period of hospitalization and seemed to have some beneficial influence on the course of the disease during radiation therapy.

CONCLUSION

Folic acid is recommended as a useful adjuvant in maintaining the hematologic well-being of patients receiving massive and prolonged radiation therapy.

Clinical Vibrometer*

An Apparatus to Measure Vibratory Sense Quantitatively

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THE clinical signs of peripheral neuropathy result from an interruption in the transmission of impulses in both sensory and motor fibers. The more common sensory stimuli used for detecting

the existence of a neuropathy consist of those necessary to elicit pain, touch, sensation of heat and cold, and vibration sense. It is well known that the more profound the disease, the greater the stimulus necessary to elicit a response in any of these sensations. Thus it would appear that any method which could quantitatively measure the threshold of the response to a stimulus would serve as a more satisfactory criterion for clinically evaluating the intensity of disease than if one were compelled to resort to conclusions based upon crude clinical perceptions.

It appears that one of the earliest functions to be disturbed in peripheral neuritis is that of vibration sense. The determination of impairment in vibratory sense may, therefore, serve as a function of impairment in the transmission of other impulses. In order to estimate quantitatively the degree of impairment in vibratory sense, one may use a vibrating instrument in which either the frequency of vibration or the amplitude of vibration can be altered.^{1,2}

We have devised a simple apparatus for estimating degrees of impairment in vibration sense by electrically activating a tuning fork which has the property of varying the amplitude of vibration while keeping the frequency constant.

This apparatus consists of a tuning fork, carrying an electromagnet on one tine, the other tine serving as the pole piece. The electromagnet is energized by a current

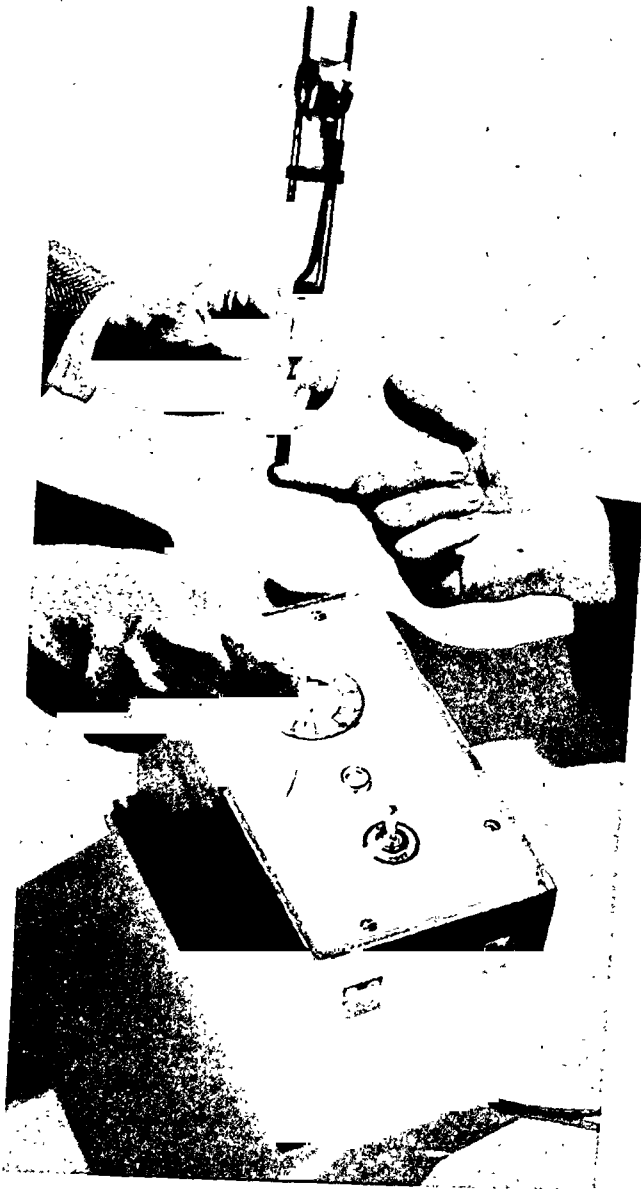
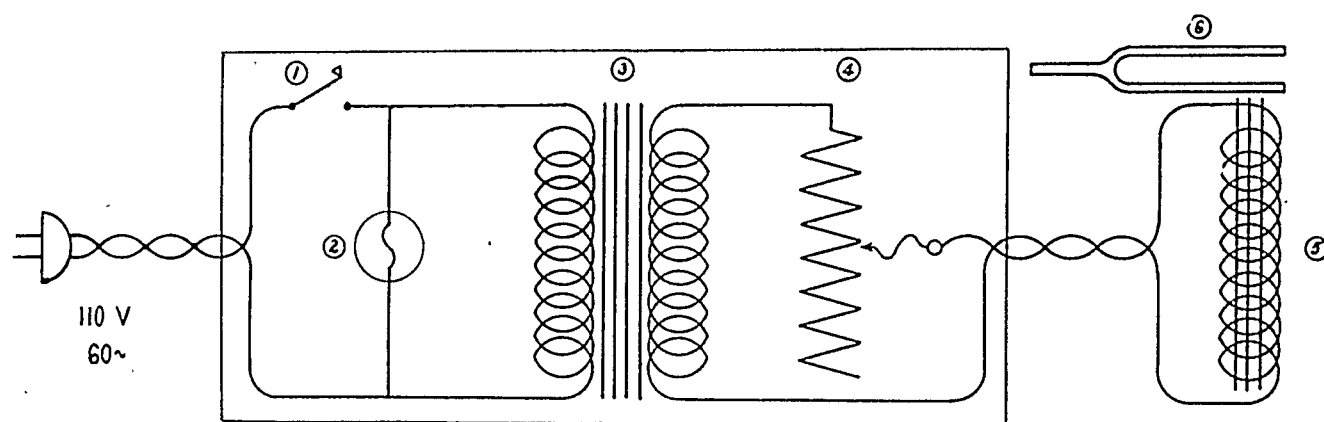


FIG. 1. Clinical vibrometer in use.

* From the Departments of Metabolism and Medicine of the Israel Zion Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York.



- 1 ON-OFF SWITCH
- 2 PILOT LIGHT
- 3 TRANSFORMER
- 4 RHEOSTAT
- 5 ELECTROMAGNET
- 6 TUNING FORK

FIG. 2. Wiring diagram for clinical vibrometer.

obtained from a 60 cycle power line. The usual 110 volt current is reduced through a transformer to 6 volts. The intensity of the current is controlled by a wire-wound rheostat. The amplitude of vibration is controlled by the rheostat which has a calibrated circular dial. The calibrations are in arbitrary units from 100 to 0, which permit duplication of any desired setting. (Fig. 1.) The wiring diagram is seen in Figure 2.

Rotating the indicator from 100 to 0, reduces the resistance in the rheostat, thus allowing for a greater amplitude of vibration in the tuning fork. We arbitrarily set the scale so that when the indicator was at 100, the amplitude of vibration was so minimal that the normal subject could just barely detect it.

We found that the normal subject was thus just able to detect vibrations produced with the resistance dial set at 90 or more, up to 100. We also found that patients who

had an impairment in vibratory sense, responded to those higher amplitudes of vibration when the resistance dial was below 90. There appeared to be a direct relationship between the degree of impairment in vibratory sense and the amplitude of vibration to which the patient responded. Thus as vibratory sense was found to be more impaired, responses were initially perceived only to such high amplitudes as were detected by the lower figures on the dial.

CONCLUSION

An apparatus is described for quantitatively measuring vibration sense.

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Impaired Vibratory Sense in Diabetes*

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PERIPHERAL neuritis is one of the most common complications of diabetes. In spite of its clinical importance, no procedure employed in the traditional neurological examination has offered the physician an opportunity to obtain a satisfactory concept of the intensity of involvement of the peripheral nerve. The

vibrometer which we have described in the previous article makes it possible to quantitate the intensity of the neuropathic state. This is predicated upon the assumption that impairment in vibratory sense is a function of impairment in the transmission of other sensory impulses in the involved peripheral nerve.

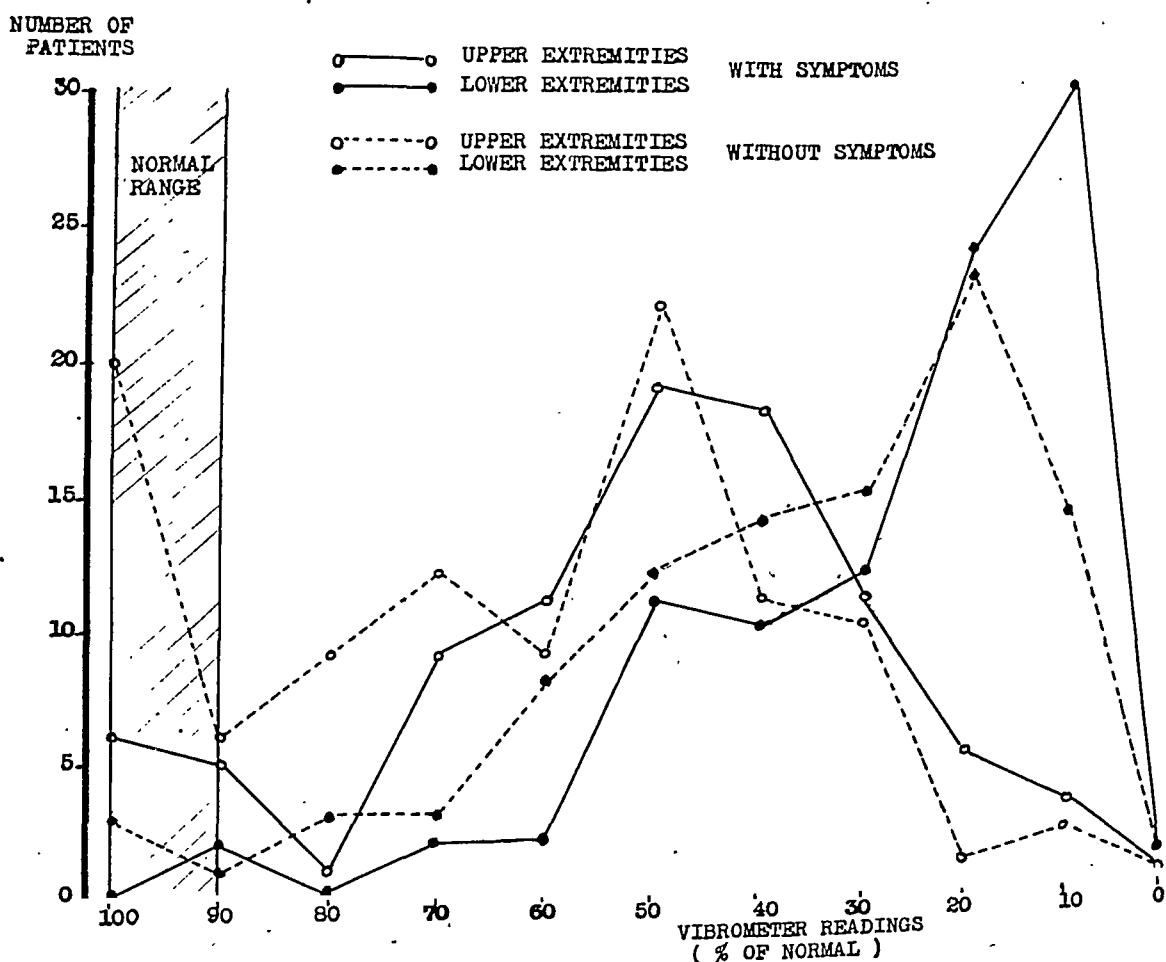


FIG. 1. Graph showing impairment in vibration sense in diabetes. Solid line represents patients with symptoms of peripheral neuritis. Broken line shows the patients without neuritic symptoms. Shaded area shows the normal zone. Shift in curve to right indicates an increasing number of patients showing more profound impairment in vibration sense. Note that the lower extremities are more severely involved in most of the cases than the upper extremities. Note also that the curve of patients without neuritic symptoms almost parallels the curve of cases with symptoms of neuritis.

* From the Departments of Metabolism and Medicine of the Israel Zion Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York.

TABLE I

No.	Age	Sex	Duration of Diabetes	Daily Insulin Dose—Units	Symptoms of Neuritis	Vibrometer Readings	
						Upper	Lower
1	13	M	2 yr.	53	None	100	70
2	16	M	3 yr.	60	None	60	30
3	18	F	9 mo.	78	None	80	60
4	13	M	3 yr.	57	None	70	60
5	19	M	6 yr.	95	None	90	70
6	12	M	7 mo.	65	None	100	100
7	11	M	1 mo.	15	None	100	90
8	10	M	2 mo.	25	None	100	40
9	23	M	9 yr.	130	None	100	100
10	17	M	11 yr.	35	None	100	60
11	8	F	2½ yr.	70	None	100	100
12	20	F	4 yr.	80	None	70	40
13	19	M	7 yr.	60	None	100	90
14	24	M	2 yr.	56	None	80	80
15	16	F	9 mo.	23	None	100	100
16	14	M	5 yr.	90	None	100	80
17	21	M	5 yr.	70	None	90	70
18	18	F	8 yr.	135	None	100	100
19	8	M	3 yr.	35	None	100	100
20	12	F	6 yr.	50	None	80	80
21	22	F	7 yr.	75	None	100	80
22	14	F	1½ yr.	42	None	100	100
23	23	M	7 yr.	90	None	90	70
24	7½	F	1½ yr.	60	None	100	100
25	12	M	6 yr.	80	None	100	100
26	13	M	1 yr.	55	None	100	100
27	16	F	4 yr.	65	None	70	50
28	21	M	4 yr.	72	None	100	50
29	8½	F	2 yr.	42	None	100	100
30	9	F	2½ yr.	128	None	100	100
31	14	M	9 yr.	72	None	100	60
32	16	M	3 yr.	100	None	100	80
33	17	F	2 yr.	100	None	100	100
34	17	M	5 yr.	35	None	100	50
35	6	F	1½ yr.	35	None	100	100
36	19	F	1 yr.	60	None	100	100
37	22	M	8 yr.	100	None	100	100
38	20	F	8 yr.	112	None	100	100
39	14	F	9½ yr.	74	None	100	100
40	22	M	3 yr.	55	None	100	80
41	17	M	4 yr.	144	None	100	100
42	7	M	3 yr.	50	None	100	100
43	16	M	11 yr.	90	None	100	100
44	25	F	9 yr.	36	None	80	50
45	20	M	16 yr.	112	None	100	80
46	24	F	22 yr.	68	None	100	100
47	15	M	2 yr.	53	None	100	100
48	19	F	9 yr.	112	None	100	100
49	22	F	5 yr.	60	None	100	70
50	23	M	3 yr.	95	None	100	70
51	17	F	6 yr.	85	None	100	100
52	13	F	2 yr.	52	None	100	100
53	13	M	2 yr.	60	None	100	100
54	20	F	2½ yr.	68	None	100	100
55	25	F	13 yr.	56	None	100	100
56	11	F	7 yr.	44	None	100	100
57	20	F	13 yr.	96	None	100	70
58	23	M	18 yr.	64	None	100	100

Recognizing that peripheral neuritis in diabetes assumes, generally, a stocking and glove distribution in the extremities without revealing any involvement according to somatic segmental levels, our plan of study consisted in testing the tips of the digits in the cases under observation. After observing that all the digits of the same limb gave approximately the same readings, it was decided, for purposes of simplicity, to record the readings on the tips of the index fingers of the upper extremities and of the large toes of the lower extremities.

This study is concerned with a determination of the threshold of vibratory sense in diabetics. Having once established the threshold of response with our instrument in 100 normal unselected individuals, we had a standard by means of which we could be guided in quantitating impairment in vibratory sense in diabetics. The first part of our study consisted in establishing these thresholds in 100 diabetics who presented classical neuropathic symptoms in the extremities consisting of one or more of the following: numbness, burning sensations, sticking pains, sensations of pins and needles, cramp-like pains, stiffness and formication. The second part of the study consisted in quantitating vibration sense in 100 diabetics who had no symptoms of neuritis. The accompanying figure (Fig. 1) is a graphic summary of these 200 cases. The ordinate is calibrated in terms of number of patients and is plotted against the vibrometer reading in the abscissa. It will be seen that in those with peripheral neuritis, there was not a single patient who revealed the existence of normal vibratory sense in the lower extremities and only two out of 100 showed normal readings in the upper extremities. It will also be observed that the majority of the cases had a much more profound impairment in vibratory sense in the lower than in the upper extremities.

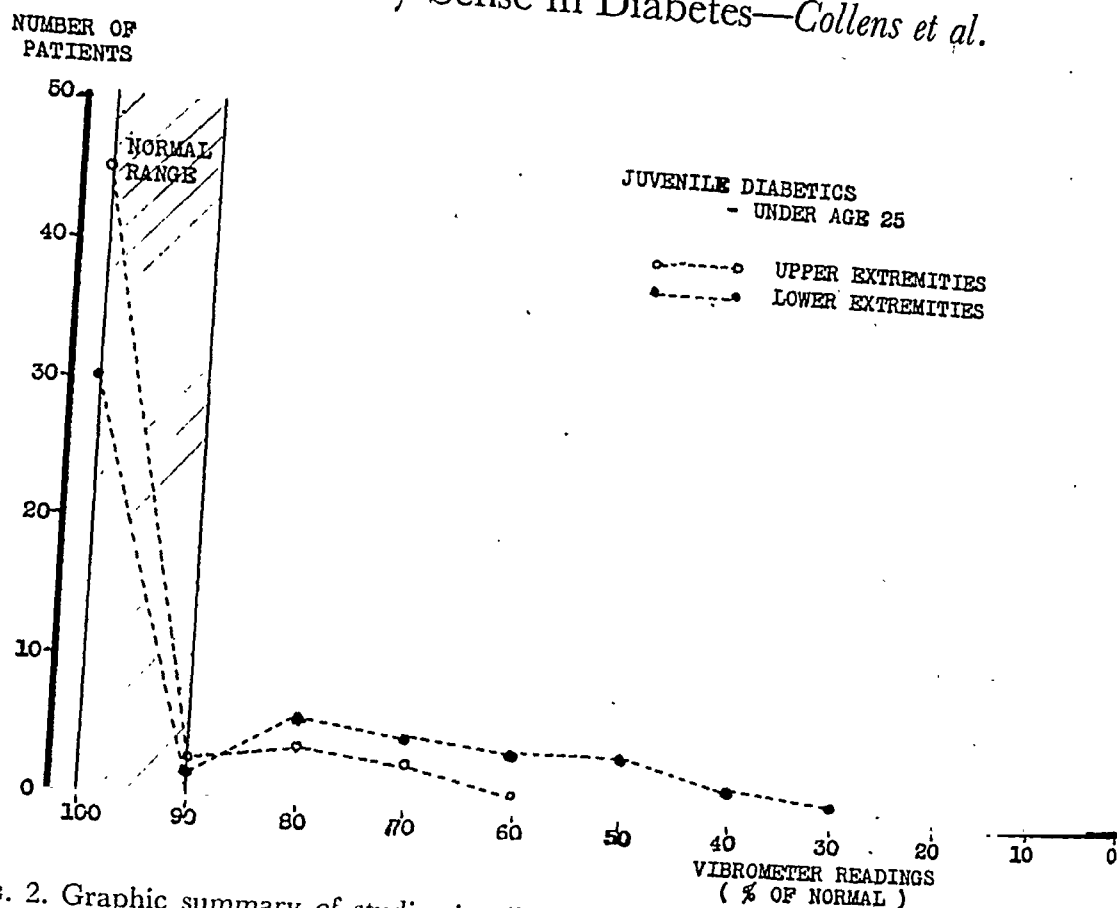


FIG. 2. Graphic summary of studies in vibration sense in fifty-eight young diabetics under twenty-five years of age. Note the small incidence of impaired vibratory sense and the mildness of the impairment.

What has proved to be most significant from this study is that diabetics who had no symptoms of neuritis whatever revealed an impairment in vibratory sense. It will be seen from the chart that only twenty-six out of 100 patients without symptoms gave normal readings for vibratory sense in the upper extremities and only four out of 100 had normal readings in the lower extremities. The remainder showed a specific impairment in vibratory sense. It is striking that the intensity of impairment in these cases is almost as great as in the diabetics with symptoms of neuritis.

It is apparent from this study that this method for testing vibratory sense has made it possible to detect the existence of a subclinical neuropathic state in diabetics who do not have symptoms of neuritis.

We then conducted a study of fifty-eight juvenile diabetics under the age of twenty-five. There are several pertinent observations in this group which, on analysis,

appear to be provocative and have upset some traditional concepts with regard to the rôle of the control of diabetes in relationship to the development of neuropathic states.

In Table I will be found a summary of these cases and in Figure 2 will be seen a graphic chart in which the number of cases is plotted against intensity of impairment in vibratory sense. The following conclusions can be deduced from these observations: First, there was not a single case who had symptoms of neuritis under the age of twenty-five; and second, the subclinical neuropathic state was found to exist in 14 per cent of the cases in the upper extremities and 43 per cent of the cases in the lower extremities. All the patients under the age of ten had entirely normal readings. There were six cases in this group. No patients had impairment in vibratory sense in the upper extremities of an intensity greater than 60 per cent of the normal and in the lower extremities greater than 30 per cent

of the normal. This would indicate that age plays a part in predetermining the development of neuropathy only past the age twenty-five.

What is most disturbing in the observations made in the juvenile group is that there does not appear to be any relation between the duration of the diabetes, the intensity of the diabetes, or the degree of control of the diabetes, and the intensity of impairment of vibratory sense. We can at this point cite the case of a female who developed her diabetes at two years of age. (Table I, Case 46.) She is now twenty-four years old and reveals normal vibratory sense readings at this date in spite of the fact that she is a severe diabetic and is satisfactorily maintained on a high carbohydrate diet with 68 units of insulin per day. On the other hand, this patient can be compared with another juvenile in whom diabetes was known to exist for only two months and vibratory sense studies revealed 40 per cent of normal in the lower extremities. (Table I, Case 8.) This child has proved to be a mild diabetic, is fully controlled and free from glycosuria, is thriving, and the total insulin requirement is 25 units per day.

We should like also to cite the severe case of a juvenile diabetic in whom the severity of the disease can be recognized by his insulin requirements which consist of 130 units per day. (Table I, Case 9.) His vibratory sense readings are entirely normal. It is interesting to mention in connection with this case that he has been diabetic for nine years and is seldom sugar-free.

Then there is also the case of a severe diabetic who has never been particularly cooperative and in whom persistent glyco-

suria and hyperglycemia have been characteristic features in spite of the fact that he has taken an average of 112 units of insulin per day. (Table I, Case 48.) He has had diabetes for nine years and his vibratory sense readings are normal. These observations have a tendency to upset our traditional concepts that adequate control of diabetes can protect the patient against the development of neuropathic states.

There is evidence that this phenomenon of impaired vibratory sense in the diabetic is reversible. This will appear in a paper on the treatment of peripheral neuropathies in the diabetic in the Proceedings of the American Diabetes Association.

CONCLUSIONS

1. Peripheral neuropathic states can exist in the diabetic in subclinical form and can be recognized by quantitative studies of vibratory sense.

2. In diabetics with peripheral neuritis, 90 per cent had impairment in vibratory sense in the upper extremities while 98 per cent had impairment in the lower extremities.

3. Impairment in vibratory sense occurs almost as frequently and almost as severely in diabetics without symptoms of neuritis as it does in those with symptoms.

4. No diabetic under the age of ten had any impairment in vibratory sense.

5. It appears from these studies that not only impaired vibratory sense but also symptoms of neuritis can develop in the diabetic regardless of the duration of the disease, the severity of the disease or the degree of control of the disease.

The Planning of a Camp for Diabetic Children

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IN the consideration of the problem of a summer camp for diabetic children, a problem which is growing and will increase as time goes on, it is believed that it is timely to bring forth the needs and the essential outlay of such a camp. It seemed unfortunate that all the advantages of a camp life had been denied to the diabetic child whose very life depended upon special medical care, restricted diet and the insulin syringe. Cognizant of this, I established a summer camp in 1929 near Cleveland for diabetic children.

The reasons were many. After the discovery of insulin, diabetic children were kept alive. They no longer presented the pitiful picture of slow starvation until death released them. But just keeping a child alive was no longer sufficient. A chance for his normal growth and development was essential. His life would have to parallel in all aspects that of normal children.

The diabetic child needs the advantage of a healthful vacation even more than does a normal child, for his daily routine is an onerous thing. The diabetic child needs the exercise which helps to metabolize his food intake. It has been discovered that exercise helps partly to replace the insulin up to a certain point, for insulin dosage can often be reduced considerably while a child is at camp.

More than other children, he is apt to be introspective and inclined to be a psychological problem. The very nature of his disease is the cause for this, as well as doting parents or unintelligent handling. By com-

munal living with many other children, diabetics like himself, he can realize for the first time that he is not alone with his problems. He has the advantage of seeing how others face theirs and solve them in healthy, normal ways.

The well controlled diabetic presents the most helpful and encouraging material with which to work. The majority of diabetic children have IQ's well in advance of normal children of the same age. By giving them the advantage of a normal outlet for their energies and initiative, their growth into responsible citizenship is assured.

Lastly, by providing a place of vacation for the diabetic child, the mother is relieved of her arduous task for a brief period in which she, too, can gain some rest and renewed strength to face the burden of the child's care when he returns home.

In the past eighteen years of Camp Ho Mita Koda's* existence, these ideas have proven beyond question its worth to the community and its invaluable service to the diabetic children. Because this camp has been the pioneer in this field, many questions have come to my desk concerning its nature and organization. In order to help others who might be interested in establishing like facilities for diabetic children, I herewith state my reasons for arriving at the present type of set-up, outlining briefly its physical aspect as well as its staff requirements.

* Ho Mita Koda is Sioux Indian and means "Welcome my friend."

CAMP SITE

The camp site is the first consideration. Should it be a separate camp, devoted just to the needs of diabetic children, or should such a camp be a small unit inserted into a general camp already existing?

There are advantages and disadvantages in both. A camp for diabetic children is a highly specialized camp, serving the needs of children as other camps do in addition to serving their medical needs. This latter presents no small item. If incorporated into a general camp, it has the advantage of a large group of children in its general program. The great disadvantage is that the diabetic child is constantly pointed out as such when little incidents occur, such as insulin reactions, the necessity of eating at a separate table, the need of laboratory work, etc. Thus the focus is on the diabetic child. This is automatically eliminated when such a child is in a camp solely for diabetics where all problems are alike. Such an association then in a general camp creates certain psychologic problems or reactions which are not desirable. It does not spare the child.

Another factor in a general camp is the maintenance of a corner in the kitchen to care for the diabetic diets. One will find in such a large kitchen more people, more confusion, more friction than when such a kitchen serves only the needs of diabetic children. It is a big load at best and should, therefore, not be made any heavier.

Thus, on the whole, I believe that it is much simpler, much more efficient, if the camp is devoted entirely to the needs of the diabetic.

THE PHYSICAL PLANT

The physical plant had to fill the following needs: (1) A central unit for all community activities; (2) sleeping quarters for campers; boys, girls; and the staff: men,

women; (3) toilet as well as bath facilities for the same.

THE CENTRAL PLANT

Main Hall. The Great Hall is the largest room in the main hall. Its focal point is a huge fireplace around which much of the program is built. The stage opens onto this room. Here children gather for talks, movies, plays and general discussions; here an occasional dance is held as well as radio programs. On rainy days, especially in the evenings, it is the chief center of activities.

Library. We realized that a library was needed in the camp. For lack of space we combined this room with the stage so that it serves a dual purpose. Here around an open fireplace is housed good literature for all age groups. The floor of the room is a foot and a half higher than in the main hall, with a wide opening to frame it as a stage when used for that purpose. It is a much needed and useful room in the planning of camp programs at night. Much stimulation can be induced for further individual initiative. Short sketches and skits, often spontaneous by the campers, are encouraged. It is stimulating as well as entertaining. The little ones try to imitate the older ones and to outdo them.

Dining Room. I have utilized a large screen porch on the main building, some 110 feet long, for dining purposes. This frees the main hall of unnecessary confusion and is much more enjoyable for it is almost out of doors. The children while eating, look out on the green lawn and trees, the fountain and the totem poles. It was essential of course that the porch be screened. While on the problem of screening, I might suggest one point: use copper screen throughout the camp. It is the greatest economy by far in the long run. All screen doors are reinforced with heavier mesh screening below where children's knees or feet have a way of opening them.

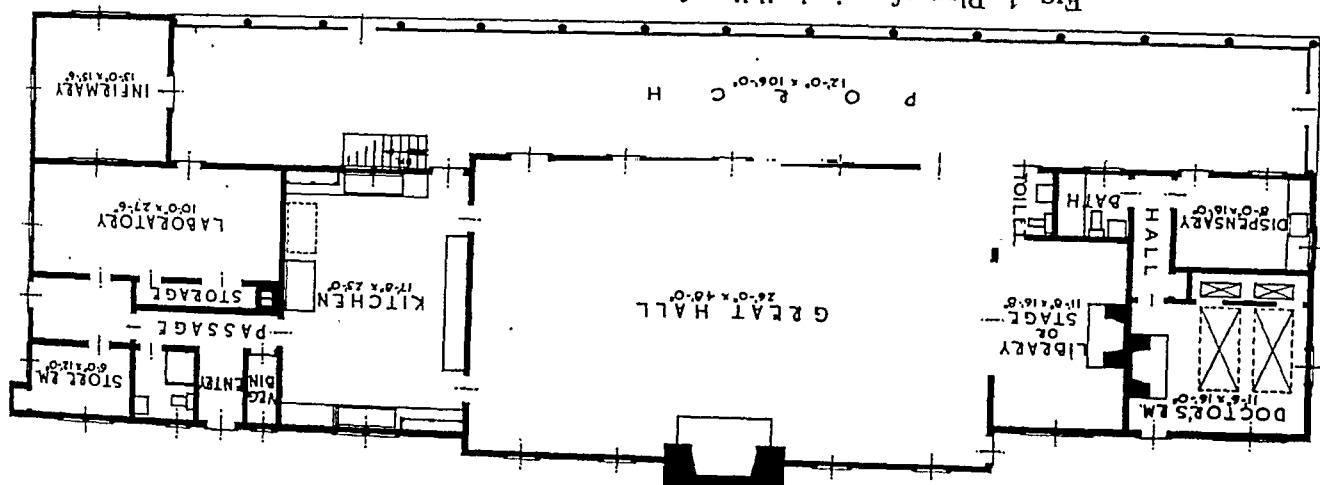


Fig. 1. Plan of main building for summer camp for diabetic children.

from among the older group of campers, serving a week or two at a time as a part of their training, measure the diet according to the outline planned by the dietitian. This assures rapid service and the food is palatable from the standpoint of its warmth. Dish washing is done in a similar manner as in hotels. The dishes are rinsed in a unit of boiling water after preliminary washing and lifted from it in racks and allowed to air dry. The wiping of dishes is against a state law, and is thus eliminated in all camps.

Refrigeration is a large item. Food for seventy to ninety people, campers and staff, takes much space. Ice refrigeration for some foods is adequate. In addition an electric refrigerator is helpful, especially when a unit has to be opened at more frequent intervals.

A small cellar under the porch is a very useful item as much of the food can be taken care of in such a cool place, for the volume of vegetables, fruits, etc., is enormous.

Hot and cold running water is provided for the kitchen by a separate heating plant attached to the main building in which the kitchen is located. Also a large screened storage room and smaller bins are needed for vegetables, fruits and staples. The disposition of the garbage may require a disposal unit unless one can arrange with some near-by farmer to haul

Kitchen. The kitchen in a diabetic camp is a very important and specialized unit. A graduate dietitian is in charge. She does all the planning, buying, measuring and supervising of all the details. Her task is easy in a general camp where the main issue is to provide good and tasty food and plenty of it. In a camp for diabetics, each individual child is on a planned diet which has to be calculated and weighed for each meal. The planning is done by the dietitian the night before in cooperation with the medical director. It is impossible in a camp of fifty to sixty children to prescribe fifty to sixty different diets, many of which would vary from each other by only a few Gm. It would be a useless waste of time. Thus diets can be grouped into about five or six routines in order to eliminate confusion. Each such diet, as a further check on its accuracy, is served on special colored plates; thus let us say, a 1,600 calorie diet is served on red plates, a 2,000 calorie diet on green plates, an 1,800 calorie diet on yellow plates, etc. This eliminates mistakes, for a child knows whether he is to get the yellow, the red or the green plates and if a wrong tray is offered him, he will immediately call attention to the fact.

A good cook under the supervision of the dietitian takes care of preparation of the food so that it is attractive, appetizing and of good nutritional value. The dietitian and her helpers, girls who are recruited

the garbage away daily. I have been fortunate to make such arrangements at my camp by agreeing to keep all paper and inedible objects separate. A small, screened unit for the garbage cans is essential a short distance from the main hall.

Infirmary. In an institution dealing with medical problems, the infirmary is a very necessary part of the set-up. Anything can happen in a camp. An infirmary meets the needs in all emergencies such as reactions, acidosis, isolation, etc. It is especially useful at night, for by removing a sick camper from the general sleeping quarters, the rest of the children are not disturbed. The infirmary and laboratory, too, are the headquarters for the night nurse. The infirmary is next to the laboratory where any needed test can be performed.

Laboratory. The laboratory is an essential part of the camp. Urine examinations, blood sugar estimations and other special tests, when indicated, are performed here. It also serves as the center of medical activity. For that reason it requires a fairly large room. The work is done by the staff consisting of a resident physician and nurses. In fact, regarding the urine examinations for instance, the question is often asked: Do the children do the urine analyses? The answer is "no." They come to camp not to be burdened with medical care of themselves. Furthermore, they do not come for instruction. That is the field of the family physician and it is not encroached upon. The camp is responsible for the medical care of the children while they are there; after that it turns them back to the family physician for his continued care and management.

We have a telephone with extensions in all vital sections of the camp.

Sleeping Quarters. Sleeping quarters are planned on the basis of the needs of this special group and on surroundings. We built units for eight to ten children. These

are open screened buildings, size 24 by 56 feet, giving ample room for cots and lockers and bedside tables. The units for girls are at some distance from those of the boys to insure privacy. In each unit children are grouped according to age. The roofs of all the buildings are insulated with celotex under the shingles which adds much to comfort during the hot summer. This point is quite essential to bear in mind.

Sleeping quarters for the staff were created in similar or in smaller units. A few small buildings accommodate husbands and wives. We have found that often young couples make good staff members. Sleeping quarters for the help, cook, assistant cook, handy man, etc., required separate small units. The quarters for the night nurse are at some distance from the general camp outlay to insure her undisturbed rest and sleep during the day.

One must bear in mind that these children require supervision at night. The night nurse must make rounds every half hour until midnight, then every hour during the rest of the night. She has to observe each sleeping cabin to see if all is well, checking to see if there are any insulin reactions during sleep. For that reason the buildings should not be too far apart. There are rainy nights. A camp on a rainy night with three to five reactions in separate buildings can present a terrific problem. Fortunately, since protamine zinc insulin came into use, this phase of the problem has been much reduced. It once was the major problem at the camp.

Toilet and Bath Facilities. It is cheaper to plan for all bathing and toilet facilities in one general building, the bathhouse, than in many separate buildings. Here again we had to provide for separate needs of campers, boys and girls; and staff, men and women. Our bathhouse is divided into four separate sections by complete partitions, each one to take care of the needs of each

of the four groups. Each room has its separate entrance from the outside and is broken down into space for toilets and another space for showers and wash stands. Hot showers, running hot and cold water and flush type toilets are provided in each of the four subdivisions. The heating unit is in the center part of the building. A septic tank provides for sewage disposal.

Water Supply. As camps are located far from the city, one has to provide for water supply. I solved this problem by drilling a well 132 feet deep, installing a deep well electric pump and a 5,000 gallon pressure storage tank underground. This has taken care of our needs adequately and efficiently.

Sewage Disposal. Sewage disposal had to be provided for the entire camp. As all the baths and toilets are housed in just two buildings, the bathhouse and the main hall, the problem was simplified. We built a large septic tank. The discharge from it, clear, unpolluted water, is lead underground to a convenient distance from the camp where it can empty into a running creek. In the kitchen, we did not forget the fat traps, as otherwise the sewage would be plugged up. Sanitary engineers helped here as state laws had to be complied with. At the close of camp each season, all water has to be drained to prevent the pipes from freezing.

Lighting. Electricity for all buildings is the safest means of lighting. It is needed also for the pump, the craft shop, etc. We were fortunate in having electricity wired into the camp. A Delco unit would have had to be installed if a utility line had not been available.

CRAFT SHOP

The craft shop is a separate building used for various activities. It is a place especially busy on rainy days. If properly conducted, it can do much for the children in teaching them to use their hands and their imagina-

tion. Here money is well spent in getting the best instructors available who can stimulate creative ability and latent initiative among the campers as well as teach them new and useful things to make.

PLAY AREA

Play space is important. The ideal acreage for a camp as set up by minimum standards of the American Camping Association is an acre per child or more. This allows for hiking, outdoor sports and activities of all types. We have provided a baseball diamond, archery court, tennis court, outdoor theatre, many camping sites and other special sites within the camping boundary.

Swimming Pool. If there is any single item of great importance during the camp season, it is swimming. It is a fine type of exercise and is refreshing. If such a camp is located on a lake or a good-sized stream, these can be utilized for this purpose. We were not so fortunate. Having no open body of water, we had to build a swimming pool. This required drilling a well for the additional water supply. To maintain the pool, all hygienic measures connected with swimming pools are carried out.

Outdoor Kitchen. Even though children are in a camp proper, they want their excursions, their hikes. Thus an outdoor kitchen at some distance from the main camp fulfills such a need. Here smaller children can have a picnic or overnight hike in order to learn primitive camping, self-reliance and improvisation as they will have to take their own insulin, cook and weigh out their own food, etc., under supervision. Yet they are within easy reach of the camp. We built our outdoor kitchen on the edge of the property. It has a roof supported by four huge chestnut uprights. The stove is of stone with ample cooking surface and a dutch oven. Other facilities are storage sheds and a pony barn.

THE STAFF

Some mention has already been made of staff members. Their duties are briefly outlined: The medical director directs the general medical care of the campers, makes any changes in insulin dosage that are indicated by blood sugar studies. He meets any medical emergencies that may arise from time to time. There is a resident physician to assist the medical director.

The nurses carry out the instructions of the physician. They give all the insulin, etc., exactly as in any hospital. The night nurse has her special duties of general supervision of the entire camp and is especially on the lookout for reactions or impending acidosis. The nurses do not wear uniforms. They wear the same type of sensible camp clothing as the counsellors for medical care and supervision, which though ever present, is kept in the background.

The dietitian has full charge of the diets, the buying of food and the serving of the meals. The cooks work under her supervision.

The counsellors have their special duties according to their assignment. Young counsellors of mature judgment are preferable as they can enter into the spirit of the camp and be a part of it. They should be of high caliber and of special training so that they will have something to offer to the children and command their respect.

A maintenance man is general utility man for the entire camp and should be responsible to the director.

CAMP PROGRAM

The camp program has developed along the most modern and progressive trends in group activity. Because of the very highly specialized medical regimen which must be adhered to for the child's safety, there is a skeleton schedule of waking, eating and sleeping, around which the rest of the pro-

gram revolves. Usually it develops as the days pass, according to the interests and inclination of the children, having no pre-camp pattern set for it. The counsellors who are highly trained, resourceful people, are capable of guiding or assisting the campers in their projects.

In this way the greatest amount of creativeness has been stimulated. The campers gain the highest degree of satisfaction from their experience because they have planned it themselves within their own groups, instead of following a predigested schedule cooked up before their arrival. Many graduate students have taken their group-work training at Ho Mita Koda.

FINANCES

To build such a camp involves a considerable investment. Just how much, will depend largely on the particular community and the cost of labor at the time. To start with it will represent an investment of at least \$50,000.00. Then there is the equipment, the upkeep and the depreciation to consider. The present worth of our camp with the equipment is about \$75,000.00. This does not include the upkeep, the depreciation and operational costs.

Let us consider the basic cost during operation as being \$5.00 per child per day. This is low when we consider the double function of the camp, the camping proper plus the full medical care comparable to hospital care. Such a camp thus has two staffs and consequently double expense as compared with ordinary camps.

If we figure on one dollar per day per person for food, we get the following figures:

A. Food—50 children	
	\$50.00 per day
23 adults	
	\$23.00 per day
Total \$73.00 × 30 is	
	\$2,190.00 per month
B. Staff Salaries—	
	\$2,405.00 per month
Total	
	\$4,595.00 per month

Income. The camp was incorporated on a non-profit basis to serve diabetic children according to their means. The top fee has been \$100.00 per month. Very few children have been able to pay this sum. Most children have paid on a sliding scale from \$100.00 to nothing. This means that supplementary sums have had to be raised to take

care of operating and maintenance costs. In the past the Cleveland Foundation, the F. P. Fenn Fund and the Rose Fund and private gifts have helped to provide the needed money.

It is an expensive proposition but worth the investment in the pleasure it provides and the concrete results it obtains.

Differential Diagnosis in Obscure Fever^{*}

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ABNORMALLY high body temperature has been the subject of study by the clinician from as far back as ancient times up to the present day. A brief résumé of the development of knowledge of the mechanism of the production of fever, a classification of those conditions commonly associated with fever and a plan of diagnostic attack will be presented.

That Hippocrates was aware of fever and its importance as a prognostic sign there can be no doubt. Fever was regarded as an expression by the body of a disturbance of its humors. Recovery resulted from the elimination of the "concocted" humors (crisis) or diminution of secretion or increase in excretion (lysis).

No outstanding contribution to the subject of fever was made after Hippocrates' time until the invention of the thermometer by Galileo between 1593 and 1597.⁷ Sanctorius, the father of the science of metabolism, began estimating the temperature of the human body with a thermometer in 1625. Although a clinical thermometer 3 inches (7.6 cm.) long was constructed by duVal in 1638, it was not accepted for general use. Between 1625 and 1745 Swammerdam, Haller and Martine kept the subject of thermometry alive from the viewpoint of physiology, but little or no clinical use was made of the instrument. De Haen in 1761 used thermometers in his clinic in Vienna.

In 1814, Davy clearly demonstrated the diurnal variation in body temperature. To Becquerel and Bréchat (1835) is ascribed

the determination of 98.6°F. (37°C.) as the normal mean body temperature.⁹ In 1850, Traube challenged the Hippocratic "doctrine of the crises" and two years later published the first temperature curve to appear in the literature. He persuaded Wunderlich,¹⁷ an associate at Leipsig, to study clinical thermometry. In the next fifteen years he studied about 25,000 patients. In 1868 he published his classic monograph and established the fact that the course of certain diseases is revealed by the course of the body temperature.

Until 1867 when Allbutt invented a self-registering mercury thermometer, the thermometers in use were ungainly and inaccurate. Wunderlich's instrument was a foot long and had to be held in the axilla for twenty minutes. Small wonder that thermometry for clinical investigation was unpopular!

With the advent of a fairly accurate method of estimating body temperature, the study of metabolism begun by Sanctorius became a major undertaking. Outstanding among the men in this field has been DuBois⁹ who first became interested in the subject when he was a hospital orderly in the Spanish-American war carrying water to typhoid fever patients. In his monograph he has shown by calorimetric studies on normal human beings that production of heat by the body always equals the loss of heat.

On the basis of many studies in which human beings, normal and diseased, were subjects, DuBois concluded that the rise in

^{*} From the Mayo Foundation, Rochester, Minn.

temperature in fever does not depend on the level of production of heat or change in production but is due to an adjustment which keeps elimination of heat below production. This adjustment is made by the temperature regulating mechanism. Liebermeister¹³ has likened this to setting the regulating mechanisms at a higher level.

The thermoregulatory centers have been fairly well localized by Ranson.¹⁴ Centers controlling loss of heat are in the preoptic and supraoptic regions between the anterior commissure and optic chiasm. The center controlling production and conservation of heat is located in the caudal part of the lateral hypothalamus. It appears to be identical with the sympathetic centers. Best and Taylor⁴ stated: "From observations of patients with intracranial lesions involving the base of the brain, it seems most likely that in man the centers are situated as described by Ranson and his associates for animals. Lesions in the supraoptic region are associated, not uncommonly with hyperthermia; hypothermia, on the other hand, may accompany lesions involving the posterior part of the hypothalamus."

The thermoregulatory centers are influenced in three ways: (1) reflexly from the skin, (2) by the temperature of the blood flowing through them and (3) by toxic substances in the blood.

Hewlett¹² stated that, "in true fever, heat regulation is present but perverted." Hence lesions of the brain involving the thermoregulatory centers are not the cause of true fevers. Actually this question is of more than academic interest in differential diagnosis since, when a patient has a constant high temperature which will not respond to the usual measures for lowering of fever, the postulation that a lesion of the brain is present is warranted.

Before consideration of the diagnosis of the cause of fever, it may be well to review the causes of elevated temperature which

are physiologic, rather than pathologic. Temperature may rise to 104°F. for a short time after strenuous exertion. A convulsion in which hysteria is the etiologic factor may cause a rise in the temperature by the same mechanism. Digestion may cause a rise of from 0.5° to 1.0°F. A low grade fever is not unusual in the first trimester of pregnancy. The temperature gradually falls to normal after this period. A rise of several degrees may result from dehydration of body tissues. Patients of whom the physician must be wary are malingerers who may raise the thermometer reading by physical means.

CONDITIONS IN WHICH FEVER OCCURS

The following classification of the pathologic causes of fever is a useful tool in differential diagnosis and includes most of the possible causes. The classification includes: (1) Congenital conditions and birth injuries, (2) trauma, (3) mechanical factors, (4) toxic agents, (5) infectious diseases, (6) neoplastic diseases and (7) miscellaneous conditions.

Congenital Conditions and Birth Injuries. Concerning these little need be said since they are relatively unimportant causes of fever. Among them may be mentioned injury to the brain at birth, but according to Hewlett this would not be a true fever if control of temperature were lost. Reports appear in the literature from time to time of cases of so-called habitual hyperthermia.¹⁵ The patients have a temperature of 99° to 101°F. (37.2° to 38.3°C.). Another condition which might be included in the congenital group is the fever associated with so-called constitutional psychopathic inferiority.¹

Trauma. Thermal reactions which occur after cystoscopy, gastroscopy or bronchoscopy, so-called fracture fevers, and the slight rise in temperature following operations when no infection is found to account for the fever may be considered to be a result of trauma. Fever may be attributed to trauma in these cases when marked

leukocytosis is absent and the fever is short lived. However, secondary infection may supervene.

Fever which occurs after crushing injuries usually begins as simple fracture fever augmented by a toxic factor from the products of tissue destruction and maintained if the toxic element is severe or secondary infection sets in.

Mechanical Factors. Fever may result from factors which act directly on the centers that control temperature. For instance, following spinal tap the lowered pressure of the cerebrospinal fluid disturbs the thermoregulatory center. Other factors may act directly on the mechanism of dissipation of heat and fever will occur. In ichthyosis heat cannot be lost from the skin by the mechanism of vaporization, although some heat may be lost by radiation by the skin.³

Toxic Agents. Fever may occur in reactions to common drugs, such as alcohol, arsphenamine, iodides, bromides, belladonna, morphine and occasionally barbiturates. The diagnosis in many drug fevers is suggested by concomitant skin rash. By far the most important drug fever today is that due to sulfonamides. In a recent six months' period in a busy city hospital no less than one fever of obscure origin resolved each month when administration of sulfonamide compounds was discontinued.

Among other toxic reactions which cause fever may be mentioned all foreign protein reactions (including transfusion reaction) and reactions to pyrogens in rubber tubing.

In a broad sense fever associated with hyperthyroidism, heart failure and heat stroke fits into this group. Death of tissue in any part of the body may liberate toxic substances which cause fever. This occurs in pulmonary or myocardial infarction.

Infectious Diseases. In the diagnosis of infectious disease, not only the usual bacterial and parasitic infections of peacetime but also the tropical diseases which were

introduced in this country during and since the war must be differentiated. Since most bacterial disease can be diagnosed readily by isolation of the offending organism and most contagious diseases by the clinical picture, this relatively large group of fever producing diseases will not be considered in detail. Diagnosis of some infectious diseases will be considered in a later section.

In the absence of any positive history or physical findings the presence of fever should suggest the possibility of hidden infection. Perinephritic abscess may not cause marked pain and may elude diagnosis until a complication, such as rupture into the kidney, occurs. Usually, however, some tenderness and spasm of the loin is present and leukocytes number from 20,000 to 30,000 per c. mm. of blood. The abscess is usually metastatic and the primary lesion, such as a small furuncle on the skin, may be insignificant.

Another difficult diagnosis is hepatic abscess. It may occur many years after an amebic infection of the colon or it may occur only a few days after a pyogenic infection such as acute cholecystitis or acute appendicitis. Confirmatory findings in the pyogenic type are pain in the region, enlargement of the liver and septic type of fever.

Although histoplasmosis is a rare disease, it would be diagnosed more frequently if it were considered as a possibility in all diseases characterized by chronicity, fever, emaciation, leukopenia and splenomegaly.

Neoplastic Diseases. Just what mechanism produces fever associated with neoplasm is open to conjecture. Undoubtedly, toxic-degenerative processes play a part but frequently no evidence of necrosis is seen in microscopic sections of the tumor. From the diagnostic point of view, the mechanism is not so important as the fact that the fever does occur. Neoplasm should be considered in all cases of fever of unknown cause but

particularly in cases in which adequate diagnostic procedures and therapeutic trials have not revealed infection. Fever may be the sole symptom for many weeks in the early part of the illness of a patient who has bronchogenic carcinoma.

In a study of 238 cases of carcinoma in various sites Briggs⁵ found that in more than a third fever was noted in some phase of the illness. He stated, however, that its occurrence as a pronounced feature of the disease is an unusual finding. He found that fever was present in 60 per cent of cases of carcinoma involving the lung and pleura. Another point to bear in mind is that a lung abscess occasionally may result from the breakdown of a neoplastic process.

Miscellaneous Conditions. At least 95 per cent of the cases in which the temperature is abnormally elevated can be classified in the foregoing six main groups. In the seventh (5 per cent of cases) fall the miscellaneous conditions in which the cause of fever is obscure. In some of these conditions the cause of fever may be toxicity, infection or neoplastic diseases associated with destruction of tissue.

Among the more important of the miscellaneous conditions are: periarteritis nodosa (fever in 80 per cent of cases),¹¹ verrucous non-bacterial endocarditis, disseminated lupus erythematosus, blood dyscrasias such as leukemia, diabetic acidosis, bleeding duodenal ulcer (fever in 80 per cent of cases), cirrhosis of the liver (in 50 per cent of cases),¹⁰ psychogenic fever and fever of unknown etiology.

Dill and Isenhour⁸ in their study of the cause of fever in cases of bleeding peptic ulcer made control studies of normal subjects. When they introduced blood into the gastrointestinal tract no fever occurred.

DIAGNOSIS

The diagnosis of an unexplained fever is one of the most difficult problems in

medicine and for this very reason one of the most interesting and satisfying to the clinician when a correct diagnosis is attained. Truly, the study of fever is the study of medicine because the cause of fever may be related to any organ or any tissue in the body.

History. As in all diseases, this is probably the most important when a clear-cut story can be obtained. Geographic location, contact with either human beings or animals that may have an infectious disease, and periodicity of fever should always be considered.

Because the geographic locations of endemic areas of disease should always be kept in mind in eliciting a history the clinician will do well, in these times, to provide himself with maps showing the endemic areas of such diseases as malaria, typhus and histoplasmosis. It is also important to ask the patient about his contact with persons who have contagious disease. Contagious diseases, particularly those in which skin rash is not present, should be considered in the differential diagnosis.

Frequently the type of temperature curve shown by observation of the patient for several days or weeks will give a hint as to the diagnosis in malaria, Hodgkin's disease (Pel-Ebstein fever) and the response of rheumatic fever to salicylates. The monograph by Ask-Upmark on periodic fever is well worth reading.²

If a veteran who has returned recently from New Guinea complains of chills and fever which occur every other day, malaria certainly would be considered as the first possibility. Brucellosis would be the first consideration when the patient is a farmer or even a city dweller whose fever began shortly after he drank unpasteurized milk. If a patient relates that he has dressed wild rabbits, the possibility of tularemia must be considered.

Probably the most important factor in establishing toxicity as a cause of fever is the history. Frequently when a patient is asked if he has taken any medicine or drugs lately the answer will be "No" but on further questioning he may say that he has been taking a tonic which frequently proves to be "Doctor So and So's nerve elixir," which contains bromides. When a patient who is not being given any medication has a fever in the immediate postoperative period, the internist will do well to bear in mind the routine at operation of placing 5 Gm. of one of the sulfonamide drugs in the peritoneal cavity or surgical wound. Fever has resulted from reaction to just this relatively small amount of the drug.

In interpreting the history the negative side must also be given consideration. Drug fever may occur although the patient has not ingested the drug by mouth. A negative history of alcoholism does not rule out cirrhosis of the liver.

Certain patients may interfere with the taking of a good history involuntarily by stressing the importance of fever when actually it causes no distress.

Physical Examination. Special attention should be given to the search for rashes, incipient jaundice, enlarged lymph nodes, nodules on vessels or in muscles, hard prostate gland, tender regions in bone, small draining sinus and pathologic fractures. In rare instances, barbiturates will cause a rash and fever almost indistinguishable from scarlet fever. In these cases it is well to isolate the patient even though the diagnosis of drug fever is the more likely one.

Laboratory Studies. Serologic studies, repeated cultures, determination of the sedimentation rate, and smear and culture of the blood often will yield important diagnostic information. In a case in which the presence of histoplasmosis is suspected, smears of the peripheral blood will at times show parasitized mononuclear cells. Sternal

puncture will reveal a greater number of positive smears. Cultures which are thought to contain *Histoplasma capsulatum* should be kept a month before being declared negative.

Urinalysis and culture of the urine should be carried out. If, for any reason, the presence of ova or parasites in the gastrointestinal tract is suspected, the feces should be examined. Erythrocyte, leukocyte and differential counts should be made. It should be borne in mind that absence of eosinophilia rules out neither periarteritis nodosa nor trichinosis. Blood agglutination tests for typhoid, paratyphoid, tularemia and brucellosis should be made when the presence of one of these diseases is suspected. The diagnosis of rickettsial diseases can be made or ruled out when the Weil-Felix complement fixation is carried out. All the rickettsial diseases are important and a positive Weil-Felix reaction should be looked for. To differentiate Rocky Mountain spotted fever from other rickettsial diseases a complement fixation test should be performed. Results become positive during the second week of the disease.

Examination of gastric washings and sputum are particularly useful in the diagnosis of tuberculosis. Neoplasms of bone and lesions due to metastasis from prostatic carcinoma may be diagnosed from the results of determination of the acid and alkaline phosphatase in the blood. Determination of the basal metabolic rate may be a useful procedure. In fevers associated with hyperthyroidism and infection the basal metabolic rate is increased. It is normal in habitual hyperthermia. It may be normal in hyperthermia due to a brain lesion.¹⁵

Several pitfalls common to the interpretation of the results of all diagnostic procedures must be borne in mind. A positive result of the agglutination or skin test for *Brucella* is not necessarily diagnostic of brucellosis. Also if the sedimentation rate

is high and results of the agglutination test are positive some condition other than brucellosis is probably present for in brucellosis the sedimentation rate is relatively low to normal.⁶ Diagnosis of brucellosis is best made by positive blood culture, for the fact that the patient has been in contact with infected animals does not necessarily mean that he has become infected.

In the absence of positive findings on examination of the sputum or gastric washings and on subsequent inoculation of guinea pigs the diagnosis of pulmonary tuberculosis is best made by means of serial roentgenograms. Negative results of examination of gastric washings on several successive days merely mean that the patient is probably not a menace to his family. They do not rule out the diagnosis of tuberculosis.

Roentgenologic Examination. Roentgenograms of the pelvis, thorax and long bones may reveal evidence of the pathologic condition which is causing the fever. Evidence of metastasis may be found in long bones and presence of stones in the pancreatic region may be noted. Roentgenologic examination of the gastrointestinal tract may be necessary to rule out the presence of a polypoid type of neoplasm which is asymptomatic until it has metastasized.

Laparotomy. Walters and Snell¹⁶ have reported a case of cholecystic disease in which intermittent fever was the only symptom. There was no jaundice, no pain and no roentgenologic evidence of stones. Yet, on laparotomy stones were found in both the cystic and the common ducts. Mention is made of this to show that sometimes laparotomy serves as a diagnostic procedure in unexplained fever. Whether it is warranted or not is a moot question.

Therapeutic Tests. Several therapeutic tests are helpful in establishing the type of fever. Fevers due to infections can be treated successfully by administration of anti-

pyretics but the temperature rarely falls when narcotics are given. The elevated temperature in habitual hyperthermia and the "neurosis" type of fever is not reduced by administration of antipyretics but is reduced when morphine or some other narcotic is given.

Antibiotic and chemotherapeutic agents can eliminate fever due to infection by terminating the infection. Administration of these agents is a standard procedure in the diagnosis of unexplained fever after drug fever has been ruled out. These drugs rarely reduce the fever unless some infection has been overlooked in the other diagnostic procedures.

Another confusing point in the toxic picture when a reaction due to the sulfonamide drugs occurs in older people is the association of cerebral symptoms which sometimes leads to a mistaken diagnosis of cerebral vascular accident. The quick recovery of these patients when they drink a glass of water every hour and are given a little sodium bicarbonate rules out the possibility of cerebral infarction. Also the blood pressure tends to stay at a fixed level in toxic reactions. A therapeutic trial of emetine may confirm the presumptive diagnosis of amebic abscess of the liver even when results of examination of the stools are negative.

Treatment with roentgen rays may be given when a presumptive diagnosis of lymphoblastoma has been made. This sometimes gives surprisingly gratifying results.

Microscopic Examination. Biopsy of a node, vessel or nodule in skin or muscle may be the only positive means of diagnosing lymphoblastoma, periarteritis nodosa or trichinosis. In a small number of cases a diagnosis cannot be made even at necropsy.

SUMMARY

True fever is due to a disturbance of the thermoregulatory centers. Fever results

when these centers keep elimination of heat below the level of production.

The usual causes of fever can be grouped under the following headings: congenital conditions and birth injuries, trauma, mechanical factors, toxic agents, infectious diseases and neoplastic diseases. This group accounts for about 95 per cent of all fevers. A few conditions which do not fit under these headings but which always should be considered in the differential diagnosis are: periarteritis nodosa, verrucous endocarditis, disseminated lupus erythematosus, blood dyscrasias, diabetic acidosis and cirrhosis of the liver.

A plan of diagnostic attack has been presented, the main features of which are: (1) critical evaluation of the history, (2) critical evaluation of the laboratory findings and (3) emphasis on alertness for evidence of malignant disease.

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Treatment of Severe Functional Headaches

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THE pathogenesis of headaches has been the subject of extensive and fruitful investigation during the past decade. A number of etiological factors have been uncovered and many of the older beliefs have been subjected to critical appraisal. For instance, the experimental studies of Eckardt et al.⁴ have shown that myopia (artificially produced) will not cause headache, contrary to common belief. However, astigmatism and hypermetropia will do so. Williams¹² recently classified sinus headaches as an allergic phenomenon involving the cranial muscles. Horton et al.⁸ have described a peculiar syndrome of headache associated with sweating, lachrymation and other phenomena which can be precipitated or reproduced by injections of histamine; in these cases the vasodilator action of histamine is said to be the causative factor. In a recent discussion of the pathogenesis of headaches Wolfe¹³ outlined the chief mechanisms as follows: (1) spasm of the cranial or cervical muscles; (2) compression, traction or inflammation of the sensory cranial or cervical nerves; (3) traction on or displacement of the large veins and adjacent dura. (4) distention, traction and dilatation of the intracranial and/or extracranial arteries. In keeping with this last mechanism are the findings of Atkinson² who believes that the scotomas of migraine are vasoconstrictor phenomena while the headache itself is a secondary vasodilator reaction.

The manifest importance of vasomotor disturbances as a factor in the pathogenesis

of functional headaches has led to the investigation of drugs which alter the cerebral circulation. The nicotinic acid group has been studied intensively both experimentally and clinically.

The free nicotinate radical is directly responsible for the vasodilator activity of sodium nicotinate, nicotinic acid, the other ionizable salts and even quinine nicotinate. The amide (nicotinamide) and the diethylamide (coramine) have no vasodilator activity.³ The vascular action of the nicotinate radical is opposed by adrenalin³ and is not synergized by prostigmin,⁹ showing that its action is directly on the blood vessels and not via the autonomic nervous system.

Moore¹⁰ studied the effect of niacin on the pial vessels by direct visualization and was able to photograph the vasodilatation it produced. Aring et al.¹ measured the cerebral blood flow and found that increased circulation persisted for as long as an hour after intravenous injection of 100 mg. of niacin.

Limited reports of the clinical value of these vasodilators have appeared in the literature from time to time. Rogers¹¹ mentioned one case of migraine in which the attacks could be aborted by 100 mg. of nicotinic acid in oral doses; Enrique⁵ described the dramatic relief of a single acute attack of migraine by 100 mg. intravenous dose of nicotinic acid. Atkinson² has reported good results in the prolonged treatment of "histamine-negative" migraines with oral and parenteral niacin. Williams¹² administered courses of oral and intra-

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muscular niacin for sinus headaches with relief in 69 per cent of seventy-eight patients. Zeligs¹⁴ recently reported twenty-five cases of malarial headaches, resistant to all the usual drugs such as ergotamine tartrate, analgesics, etc. One hundred mg. doses of niacin provided complete relief in 40 per cent, moderate relief⁶ in 32 per cent.

In a recent paper, one of us (J. W. G.) reported the results of treatment of 100 consecutive cases of severe headache, regardless of etiology, with sodium nicotinate intravenously. Seventy-five per cent were completely relieved by a single injection and 9 per cent had only minimal recurrence within 24 hours. Since the publication of these data we have treated a considerable number of patients with migraine, and severe idiopathic headache, and a few more patients with cephalalgia following lumbar puncture. The results have continued to be as favorable as previously reported. This later material, however, could not be followed as closely nor investigated as carefully as the hundred original cases and hence does not lend itself for statistical comparison.

There is another factor in the pathogenesis of migraine and related headaches which is of the greatest importance. It has been shown⁷ that there often is an easily demonstrable disturbance of tissue hydration (i.e., salt and water metabolism) in patients suffering from such headaches. It is a generally recognized fact that migraine occurs more commonly during the premenstrual period and during menopause, when disturbances of salt and water metabolism are nearly always present. In a series of 150 cases of migraine and migraine-like headaches which were submitted to electrolyte balance studies, it was found that 90 per cent of the patients showed definite water retention and 84 per cent showed retention of sodium chloride under the conditions of a salt tolerance study. Cor-

rection of the metabolic disturbance resulted in complete cures in 44 per cent, great improvement (reduction of headaches to mild, occasional attacks) in an additional 25 per cent, improvement in 21 per cent and failure in 10 per cent.

THERAPEUTIC APPLICATIONS

Appreciation of the importance of these two factors (i.e., vasomotor disturbances and changes in tissue hydration) has led to many innovations in the methods of headache therapy and to increased efficacy of treatment.

Intravenous sodium nicotinate may prove to be a valuable therapeutic tool if used with discretion. Indications for its use are as follows:

1. It must always be kept in mind that such vasodilator therapy is purely symptomatic, and as far as we know, will not alter the severity or frequency of subsequent headaches in patients suffering from migraine or other recurrent forms of functional cephalalgia.

2. Intravenous sodium nicotinate should be used only for severe headaches. A patient with a mild headache will not be thankful for the manifest discomfort of the flush and thermesthesia which an intravenous dose of 100 mg. will produce.

3. It appears that such vasodilator therapy is particularly effective in the immediate treatment of migraine and migraine-like headaches, as well as of those following lumbar puncture, air encephalography or similar procedures. At the present time we believe that sodium nicotinate is to be preferred to the usual drugs employed in these conditions. There is no other way short of the use of powerful narcotics to alleviate the headaches following a lumbar puncture. The use of ergot derivatives such as ergotamine tartrate and ergonovine is subject to certain disadvantages. A relatively large proportion of patients do not tolerate these

drugs well; the gastric symptoms may be most distressing. The danger of ergot poisoning, though remote, must always be kept in mind when dealing with patients who suffer chronically with migraine. By way of contrast, sodium nicotinate is a non-toxic drug: 1,000 mg. per kilo body weight may be given to dogs for prolonged periods without any ill effects. In man, slight nausea may be felt during the flush; very rarely actual vomiting occurs. We have seen only a single instance of this reaction.

Contraindications to the use of sodium nicotinate are few. As already pointed out, it is too potent an agent to be used in mild headaches. The other feature which must be considered is that of dosage. The 100 mg. intravenous dose which we have used was selected arbitrarily as being large enough to produce vasodilatation in almost every instance. It may be wise, as with every other drug, to suit the dose to the patient, those with evidence of vasomotor instability (such as blushing on slight psychic stimulus, etc.) requiring smaller doses.

We have not found oral therapy to be of value.

The second aspect of the therapeutic approach aims at correcting the underlying salt and water imbalance if present. Clearly, such therapy is not merely symptomatic but is directed at an underlying etiological factor. Correction of this factor may bring about permanent alleviation of the recurrent headaches. The presence of salt and water retention may be demonstrated quite simply by the salt tolerance test. This is carried out as follows:

The patient is instructed to eat and drink exactly the same things, in identical quantity, for two consecutive days. Separate twenty-four-hour urine specimens are collected on these days. At 10 A.M. of the second (test) day the patient is given 10 Gm. of enteric-coated salt tablets and 250 cc. of water to drink. Total urinary chloride ex-

cretion on both days is determined by the usual laboratory method. If the patient does not excrete at least 7 Gm. more salt on the second day, and if he does not put out 200 cc. more urine on the second than on the first day, definite salt and water retention is present.

Salt and water retention can be demonstrated, appropriate therapy will give excellent results in at least 70 per cent of cases. Therapy is aimed at reduction of tissue salt and water as well as at decrease in vasomotor instability. The means by which this may be done are as follows:

1. High-protein, low-carbohydrate diet. High protein diets are definitely diuretic, partly because of their purine content and partly because of the resulting stimulation of certain endocrine glands. Carbohydrates, on the other hand, are antidiuretic, possibly by stimulating increased insulin production. Underweight patients should receive adequate supplements of fat to prevent any undesirable loss of weight.

2. Limitation of fluids to 1,500 cc. per day.

3. Reduction of dietary salt intake to an absolute minimum.

4. Diuresis for simultaneous removal of water and tissue salt. This is accomplished by alternate weekly courses of ammonium chloride 0.5 Gm., three times a day, and potassium acetate or gluconate 0.5 Gm., three times daily. In severe cases, injection of small doses of posterior pituitary extract may be valuable, for the transient antidiuretic effect of this hormone is followed shortly by an increased excretion of sodium chloride.

5. A combination of atropine (0.2 to 0.3 mg.) with phenobarbital (15 mg.) three times a day should be used to combat vasomotor instability.

A therapeutic response to this regimen, as evidenced by a diminution in the frequency and severity of the headaches, should be-

come apparent within about two weeks. During this time attacks may be treated with sodium nicotinate as outlined above. The dehydration routine should be maintained rigidly for at least two months, after which treatment may gradually be reduced and eventually withdrawn. However, the basic features of this antiretentional regimen, namely, fluid and salt restriction as well as high-protein, low-carbohydrate diet, should be continued by the patient. Attention to these dietary limitations should not prove overburdensome to the patient, especially when it means freedom from incapacitating headaches.

There is a type of migraine patient who develops attacks premenstrually, yet contrary to the findings in the majority of these cases, performance of the salt tolerance test shows no retention of salt. As a matter of fact, the sodium chloride excretion of these patients on an unlimited diet is usually quite high, well above 10 Gm. per twenty-four hours. These patients, who are underweight as a rule, do not respond to the treatment outlined above, quite in accord with the theory which does not lead us to expect beneficial results from further increased losses of sodium chloride. Hence we tried a different approach in a small group of such cases: Adrenal cortical extract was administered both orally and parenterally a few days before the expected attack. This treatment successfully prevented the onset of migraine headaches in all twelve patients in which it was tried.

The number of observations so far is much too small to draw conclusions, nor do the data available at present explain the mechanism by which the cortical hormone interferes with the development of a migrainous state. The well established antihistamine effects of the cortical hormone deserve consideration. One could also propose, as another explanation, that the cortical hormone accomplishes results by

correcting disturbances of electrolyte metabolism. In the meantime, until further data become available to establish a sound basis for hormonal therapy, the use of this experimental approach seems justified in migraine cases of the premenstrual type in which salt retention is not demonstrable by the salt tolerance test.

The indications for each of these methods of therapy are quite clear. Vasodilator therapy is indicated for the isolated episode of severe cephalalgia, especially following lumbar puncture or similar procedures. It is also used to alleviate migrainous attacks while the slower acting therapy of antiretentional regime is brought into play. The intelligent combination of these two procedures should provide both symptomatic relief and permanent therapeutic effect in most cases of migraine.

CONCLUSIONS

1. The mechanisms involved in the production of headaches are reviewed briefly and the importance of vasomotor changes and disturbances in tissue hydration are discussed.
2. Methods of therapy based on the correction of these two factors are outlined on the basis of two series of 100 and 150 patients, respectively.

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Seminar on Antibiotics

Penicillin in the Treatment of Syphilis*

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SYPHILIS is a disease of such exquisite and capricious chronicity that an evaluation of the ultimate results of any form of therapy requires a prolonged period of post-treatment observation. Penicillin has been used in the treatment of syphilis for but a few years. Hence, discussions of its use in this disease necessarily must be tempered, being subject to revision perhaps even in the immediate future.

Factual data on penicillin in syphilotherapy have accumulated with meteoric rapidity. This has been possible only because it has been studied on a cooperative and integrated nationwide basis. In September 1943, only three months after Mahoney's original report¹ that *T. pallidum* is susceptible to the action of penicillin, a cooperative study of the effect of penicillin in the treatment of syphilis was organized under the auspices of the Committee on Medical Research. Participating in this study are forty-one clinics and eight laboratories of experimental syphilis. As a result of their collective efforts, an enormous amount of information has been compiled. In the first three years approximately 35,000 patients were treated, and the results (for early syphilis) reported to a central statistical unit. With these significant data available, preliminary evaluations of the early results of penicillin therapy are possible.

Even the most skeptical observer no longer denies that penicillin is a valuable

adjunct to syphilotherapy, nor that it is, in some respects, superior to any previous form of treatment. That it has serious limitations is recognized by its most ardent protagonists.

The *ideal treatment* of syphilis would be that which is: (1) completely and uniformly effective, (2) entirely devoid of toxicity, and (3) readily administered with a minimum of inconvenience to the patient and to his physician.

Penicillin is effective, but not uniformly nor always completely so. It is, in marked contrast to metal chemotherapy, non-toxic, approaching the ideal in this respect. It is relatively easy to administer, and therapeutically effective amounts can be given in a comparatively brief period of time.

The principal *advantages* of penicillin in the treatment of syphilis are: (1) its lack of toxicity, and (2) the fact that the therapeutic schedule need not be inordinately prolonged. Consequently, the full course of treatment is almost invariably completed. This is not the case with any form of arsenotherapy in which toxic reactions increase in frequency the more the time interval is compressed, and in which case-holding becomes increasingly difficult as the duration of therapy is prolonged.

Penicillin is a relatively innocuous substance. The untoward reactions thus far reported to have followed its use have been confined almost exclusively to allergic manifestations in the skin.² These reactions

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Penicillin in Syphilis—Reynolds

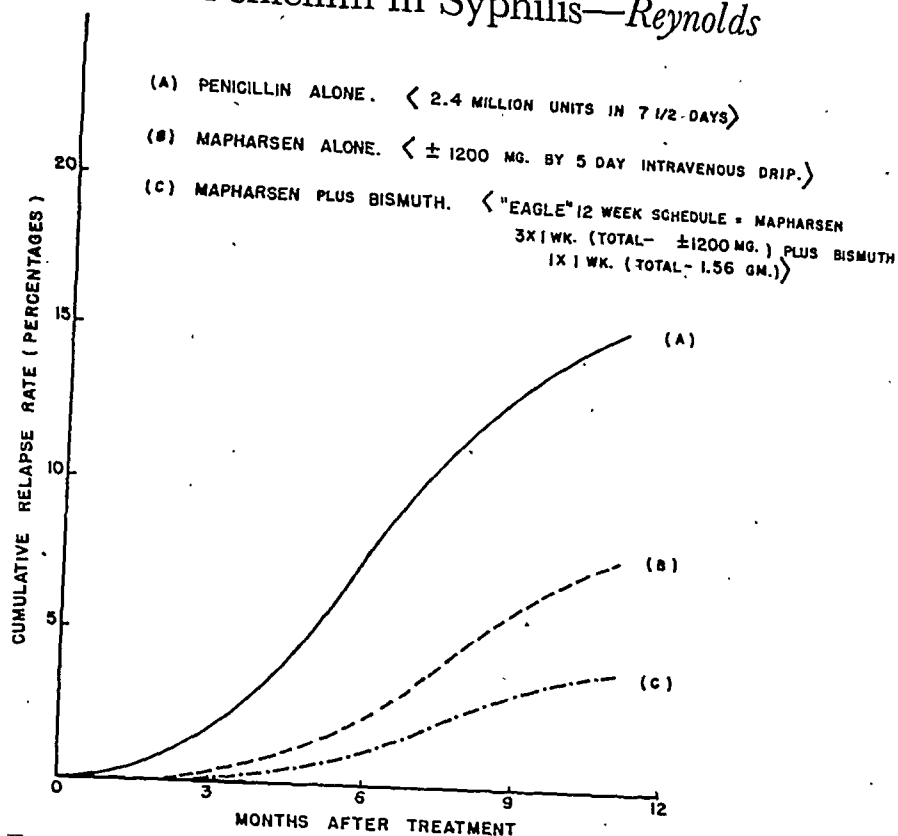


FIG. 1. Cumulative percentage relapse rates with treatment schedules utilizing; (A) penicillin alone (2.4 million units); (B) mapharsen alone (1,200 mg.); and (C) mapharsen (1,200 mg.) plus bismuth (1.56 Gm.). USPHS data, smoothed curves.

may occur shortly after the institution of therapy as a result of a pre-existing hypersensitivity, or late in the course of treatment because of developing dermal sensitization. Delayed "serum-sickness-like" reactions occur, but are extremely rare.³ The incidence of serious toxic reactions is negligible, for in less than one patient in several thousand⁴ treated for early syphilis with penicillin do untoward reactions necessitate interruption of the course of therapy. Herxheimer reactions are frequent, especially in early syphilis, in which approximately 75 per cent of patients treated develop fever with transitory intensification of the early tissue reaction. Milian's syndrome ("Erythema of the Ninth Day") has not been reported.

The principal *disadvantages* of penicillin therapy (at least with any schedule of administration the results of which are presently available) are: (1) the probable essentiality of hospitalization, when the drug is given in aqueous solution, and (2) the significant number of treatment failures

(relapse and seroresistance in early syphilis, sub-maximal improvement in certain forms of late syphilis).

The necessity for hospitalization of patients receiving penicillin as therapy for syphilis significantly reduces its general utility, for the number of hospital beds available for this purpose is limited. The United States Public Health Service has done much to obviate this difficulty through its in-patient Rapid Treatment Center program. Nevertheless, there are many to whom the necessary hospital facilities are denied.

To be feasible for ambulatory syphilis patients in the clinic and in the physician's office, a modified penicillin with prolonged activity is required. Many attempts have been made to extend the duration of penicillin action, either by delaying its absorption or by blocking its renal excretion. By far the most satisfactory modification presently available is the suspension of penicillin in peanut oil and beeswax devised by

Romansky and Rittman.⁵ With a preparation containing 300,000 units of calcium penicillin with 4.8 per cent beeswax contained in 1 cc. of peanut oil, detectable blood levels can be maintained for approximately twenty-four hours following a single injection in 75 per cent of the patients treated.⁶

Penicillin in oil and beeswax ("POB") has been used in the treatment of syphilis. Preliminary reports^{7,8} suggest that the results may be sufficiently satisfactory to warrant more widespread application. Treatment schedules utilizing POB alone and in combination with mapharsen or bismuth currently are being evaluated by the clinics cooperating in the nationwide syphilis study.

With any schedule of penicillin administration thus far studied, the incidence of infectious relapse and of seroresistance (in early syphilis) has been significantly higher than those with "adequate" metal chemotherapy. For example, the incidence of infectious relapse following 2.4 million units of penicillin in seven and one-half days has been approximately *five times* that with a twelve weeks' semi-intensive course of mapharsen and bismuth. (Fig. 1.)

Comparative ineffectiveness of penicillin is less than appears from this figure. Present information indicates 2.4 million units is a small total dosage and seven and one half days a brief period for administration. The data are for commercial penicillin; the therapeutic value of some is now known⁹ to have been low because of its high content of penicillin K. This fraction, although active *in vitro* against the test strain of *Staphylococcus* used to determine its potency in terms of Oxford units, is destroyed in the body to a significant degree,¹⁰ and is known to be decidedly inferior to other penicillin fractions in the treatment of experimental rabbit syphilis.¹¹ Also, the comparison of relapse rates following penicillin treatment

with those of metal chemotherapy must be made with the knowledge that the recorded percentage of relapse refers only to those who actually completed the full schedule of therapy. Not indicated in Figure 1 is the fact that a sizeable proportion of patients who undertake ambulatory arsenobismuth therapy become delinquent, and fail to receive the full course of treatment.

A more satisfactory comparison between penicillin and metal chemotherapy in the treatment of (early) syphilis may be made by taking into account the three attributes of the "ideal" therapeutic agent: effectiveness, lack of toxicity and convenience of administration. (Table I.)

TABLE I
A COMPARISON OF PENICILLIN WITH METAL CHEMOTHERAPY
IN EARLY SYPHILIS, IN RESPECT TO EFFECTIVENESS,
TOXICITY AND CONVENIENCE TO THE PATIENT

	"Effectiveness" (as relapse rates after 11 months) Per Cent	"Toxicity" (as deaths due to treatment)	"Convenience" (as per cent of patients completing full course of therapy) Per Cent
Penicillin 2,400,000 units in 7½ days (40,000 units × 60).	15.3	0	99.9
Intensive Arsenotherapy Mapharsen 1200 mg. in 5 days by intravenous drip.	8.5	1 in 200 ¹²	96.5 ¹³
Semi-intensive Arsenobismuth Therapy Mapharsen 3 × 1 week (total 1200 mg.) Bismuth 1 × 1 week (total 1.56 Gm.)	3.5	1 in 2000 ¹²	37.5 ¹⁴

Penicillin Resistance. Dunham, Hamre and Rake¹⁵ have suggested, on the basis of animal experiments, that penicillin-resistant

strains may be developed by inadequate initial dosage. Tsun and Frazier,¹⁶ however, report that spirochetes (Reiter strain), exposed *in vitro* to gradually increasing concentrations of penicillin, do not become less susceptible to its antibiotic action.

Thus far at least, penicillin-resistant strains of *T. pallidum* have been no serious clinical program. The only report of early lesions failing to heal under penicillin therapy is that of Tyson,¹⁷ whose patient received 2.4 million units for seropositive primary syphilis over a period of *four days*, hardly a long enough time upon which to adjudge failure of response.*

On the other hand, lesions resistant to arsenobismuth therapy may heal satisfactorily with penicillin, as Nelson and Duncan¹⁸ have demonstrated in their report of six such cases from this clinic.

PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS

The major effort of the cooperative study thus far has been to define the usefulness of penicillin in the treatment of early acquired syphilis,¹⁹ and in this condition information of some statistical significance is now available. There are, in early syphilis, several well defined end-points from which conclusions may be drawn: (1) the disappearance time of spirochetes from infectious lesions, (2) the healing of lesions, (3) the attainment of seronegativity and (4) the incidence of clinical and serologic relapse, most of which occur within the first year.

How good is penicillin in the treatment of early syphilis? There can be, of course, no simple and unqualified answer to this question, for there are several factors which influence the results of therapy. Among these are: (1) the duration of the disease, (2) the time-dose relationships, (3) the total

penicillin dosage, and (4) the concurrent use of other antisyphilitic drugs.

Duration of Disease. As with all other forms of therapy, the earlier in the course of syphilitic infection penicillin is started the better will be the results. The common denominator appears to be the total number of invading organisms within the body of the host. In the cooperative study, the failure rate when the disease was of at least two months' duration was twice that among those treated within the first week of the disease. In the U. S. Army,²⁰ the failure rate in secondary syphilis was more than four times that of patients treated in the primary stage.

Time-Dose Relationships. There is ample evidence, both from the clinic²¹ and from the laboratory²² that the therapeutic effectiveness of penicillin is profoundly influenced by the method of its administration. In this respect, penicillin differs greatly from the arsenicals. The latter, being bound by the organisms of syphilis, are spirocheticidal in proportion to the amount of arsenic so bound,²³ which is in turn dependent upon the total quantity of arsenical to which the spirochetes are exposed. Thus, a higher arsenical concentration of short duration is as effective as a concentration half as great but maintained for twice as long.

Penicillin, on the contrary, is not bound by spirochetal organisms, and its activity depends upon *the length of time during which therapeutically effective levels are available* at the site of action. Precisely what the minimum effective level is and how long it must be maintained have not been determined. It is clear, however, that penicillin is actively spirocheticidal in extremely low concentrations. It also is evident that relatively low concentrations acting over a long period of time are far more effective than high concentrations of brief duration. Increasing the tissue levels of penicillin, by giving higher dosages per injection, tends to increase its

* We have recently observed a patient with a gumma of the penis that failed to heal with 4.8 million units of penicillin given over 15 days. The lesion healed promptly following therapy with mapharsen and bismuth.

therapeutic effectiveness in the treatment of syphilis, at least up to a certain point; but of far greater importance appears to be the time period over which *T. pallidum* is exposed to the action of the drug.

It has been presumed, largely from experiences with more acutely lethal infections, that in the treatment of syphilis it is desirable to keep the tissue levels of penicillin relatively constant throughout the course of treatment. Were this true, there would appear to be a theoretic advantage in administration by continuous infusion, either by intravenous or intramuscular drip. These methods, however, necessitate markedly restricted activity on the part of the patient, and may cause painful local reactions. In view of evidence²⁴ that blood levels following intermittent intramuscular injection are not markedly inferior to those of continuous infusion, and since satisfactory results have been obtained with the former method of administration, continuous parenteral administration seems neither necessary nor especially desirable.

Indeed, there is some evidence that constant maintenance of tissue levels may not be essential in the treatment of (experimental rabbit) syphilis. Eagle reports that in these animals, the interval between injections may be prolonged far beyond the usually recommended three-hour period without sacrificing therapeutic activity. He suggests that this is possible because *T. pallidum*, unlike many pathogenic bacteria, multiplies so slowly that a considerable period of time may elapse without a significant interim increase in the number of organisms. There is no clinical information to parallel this finding, although a favorable early response has been observed in small series of patients^{25,26} treated on an ambulatory basis with aqueous solutions of penicillin, by schedules involving relatively long periods between injections during which no penicillin activity would be expected.

Total Penicillin Dosage. It is apparent from the above considerations that increased total dosages of penicillin will influence the results of therapy more if used to prolong the course of treatment than if given to augment the blood level at any one time.

With the time factor constant, the clinical results indicate a higher "cure" rate following 1,200,000 units than after 600,000 units. Results with 2,400,000 units are superior to those with 1,200,000, but the difference is less striking. With larger doses, there still are insufficient data, but with 4.8 million and 9.6 million units, it may be that the law of diminishing returns will become apparent.

Concurrent Use of Other Antisyphilitic Drugs. Eagle and his co-workers²⁷ have demonstrated that when penicillin and mapharsen are administered concurrently to syphilitic rabbits the therapeutic effects not only are additive but actually synergistic. A similar synergism between penicillin and bismuth also has been suggested.

This important laboratory observation has been studied by the clinics cooperating in the Penicillin Study, and the clinical results following the use of penicillin with mapharsen have been superior to those with penicillin alone.¹⁹ Administered in combination with bismuth, the results also are better than with penicillin alone. So significant does the U. S. Public Health Service consider this development that at its various Rapid Treatment Centers, the concomitant administration of penicillin, mapharsen and bismuth now is used routinely.

Recommendations for the Use of Penicillin in Early Syphilis. It is possible, on the basis of the facts now available, to outline in general terms certain recommendations for the use of penicillin in the treatment of patients with early syphilis. These are personal, and, as will be seen, involve both larger total dosage and longer duration of treatment than in previously published papers.

It is most convenient to start with an arbitrarily selected total penicillin dosage, which for seronegative primary syphilis should be a minimum of 3.0 million units; for seropositive primary syphilis, at least 5.0 million units; and for secondary syphilis, no less than 7.0 million units. Preparations with a minimal content of penicillin K are essential. Repeated intramuscular injections are preferred to other technics of administration.

With Aqueous Penicillin:

1. Hospitalization and administration throughout the day and night is desirable, if only to shorten the duration of treatment for the sake of convenience and case-holding.

2. Individual injections probably should not exceed 50,000 units. Further increases in the dosage per injection probably entail a progressive waste of penicillin.

3. A satisfactory interval between injections is three hours. When the time factor is important to the patient, the interval may be compressed to two hours, although perhaps at the expense of a slightly higher failure rate.

4. The total duration of treatment under these conditions would be *at least*: (1) seronegative primary, $7\frac{1}{2}$ days, (2) seropositive primary, $12\frac{1}{2}$ days, and (3) secondary, $17\frac{1}{2}$ days.

*With Penicillin-Oil-Beeswax:**

1. May prove to be feasible for use in the out-patient clinic and in the physician's office.

2. Tissue concentrations can be maintained for reasonably long periods of time in most cases with single daily intramuscular injections of 300,000 to 600,000 units each.

* It should be stressed that as yet there are available no significant data to support *any* arbitrary scheme for the use of POB in the treatment of syphilis. Unit for unit, POB may, in my opinion, be expected to prove inferior to comparable amounts of aqueous penicillin given in divided doses every two to three hours. Hence, not only should larger amounts of POB be used, but the total duration of therapy should be longer than with aqueous penicillin.

3. Occasional brief (twenty-four-hour) lapses in treatment (e.g., on Sundays when hospital clinics are closed) theoretically should detract little from therapeutic effectiveness.

4. The total duration of treatment probably should be at least: (1) seronegative primary, 10 days, (2) seropositive primary, 17 days, and (3) secondary, 23 days.

Whether metal chemotherapy should routinely be given concomitantly with the course of penicillin is largely a matter of personal preference. There is ample evidence that the combination is more effective than is penicillin alone. It is recognized, however, that the administration of arsenicals introduces a risk of serious reactions in direct proportion to the total amount of the drug, and in inverse proportion to the time interval over which it is given.

In view of this and other considerations, opinion is divided as to the desirability of combining penicillin and mapharsen in the routine treatment of early syphilis. The opinion of a majority of a group of competent syphilologists¹⁹ acting in an advisory capacity to the National Institute of Health is that the results of penicillin alone, when administered in adequate amounts over a long enough period of time, are satisfactory in a sufficiently large proportion of patients to justify eliminating arsenicals from the *original* course of treatment, reserving its use for relapsing cases. Schoch and Alexander²⁸ believe that a combination of penicillin and bismuth offers a satisfactory compromise, one which increases therapeutic effectiveness without significantly adding to the risks of therapy.

Whatever schedule of therapy is used in the treatment of early syphilis, it is essential that the outcome be determined by frequent post-treatment observations. Follow-up studies, including careful examinations for clinical evidences of relapse and serial quantitative serologic tests, should be made monthly during the

first year, and at gradually increasing intervals thereafter. The spinal fluid should be tested approximately six months following the completion of treatment.

Effect upon the Evolution of Syphilis of Small Doses of Penicillin. In penicillin a drug effective against both syphilis and gonorrhea is available for the first time. This fact raises the cogent question of the effect upon simultaneously acquired syphilitic infection of small doses of penicillin such as are used in the treatment of gonorrhea.

There is evidence that small doses of penicillin may either (1) prolong the incubation period and delay the serologic response, (2) modify or suppress completely the early tissue reaction, or (3) actually abort the disease.

Under these circumstances, patients with gonorrhea who also have suggestive signs of early syphilis should not receive (small doses of) penicillin until the possibility of a dual infection can be excluded. The presence of pre-primary syphilis should be seriously considered when patients receiving penicillin therapy for gonorrhea develop a constitutional reaction with fever, headache and malaise, which often is indicative of a Herxheimer reaction.^{29,30}

All patients treated for gonorrhea with penicillin should be followed for at least four months, and periodically checked with examinations to detect clinical manifestations of early syphilis and with reliable serologic tests.

PENICILLIN IN NEUROSYPHILIS

A proper evaluation of the results of therapy in neurosyphilis requires: (1) an understanding of its spontaneous evolution in the absence of treatment of any kind, and (2) a valid comparison between groups of treated and untreated patients. Neither of these two requisites can be entirely fulfilled. The course of untreated neurosyphilis is imperfectly understood, and there is avail-

able no group of untreated patients upon which to base a valid comparison. Moreover, there are few objective measures of "improvement" upon which penicillin can be compared with older forms of treatment.

The problem of evaluating the results of therapy in neurosyphilis is not new. It was well recognized by Wagner-Jauregg and his associates as they sought to assess the results of malarial therapy. Years of study convinced them that the efficacy of treatment in neurosyphilis should be determined solely by the response of the cerebrospinal fluid, and not at all by the clinical data, the proper interpretation of the latter being a matter of extraordinary difficulty. In the spinal fluid, the cell count and total protein content appeared to be of greatest significance, for in their experience, clinical progression rarely was observed when these two tests were normal.

Thus the concept of spinal fluid "activity" evolved, so ably championed by Dattner, Thomas and Wexler³¹ as the only satisfactory expression of the adequacy of treatment in neurosyphilis. Briefly expressed, the "Dattner-Thomas concept" is, that if the spinal fluid cell count and protein become and remain normal following treatment, the active process in the central nervous system has been rendered inactive and non-progressive, regardless of whether there has been any manifest clinical improvement. Such patients, they believe, need not be re-treated. Contrariwise, if treatment fails to reduce the spinal fluid cell count and protein content to normal, or if, having once become normal, one or both of these tests again become abnormal, the process within the central nervous system is considered to be "active." The patient, thus potentially subject to progression or relapse, requires further treatment.

Effect of Penicillin upon Cerebrospinal Fluid Abnormalities. Therapy with penicillin results in improvement in the spinal fluid

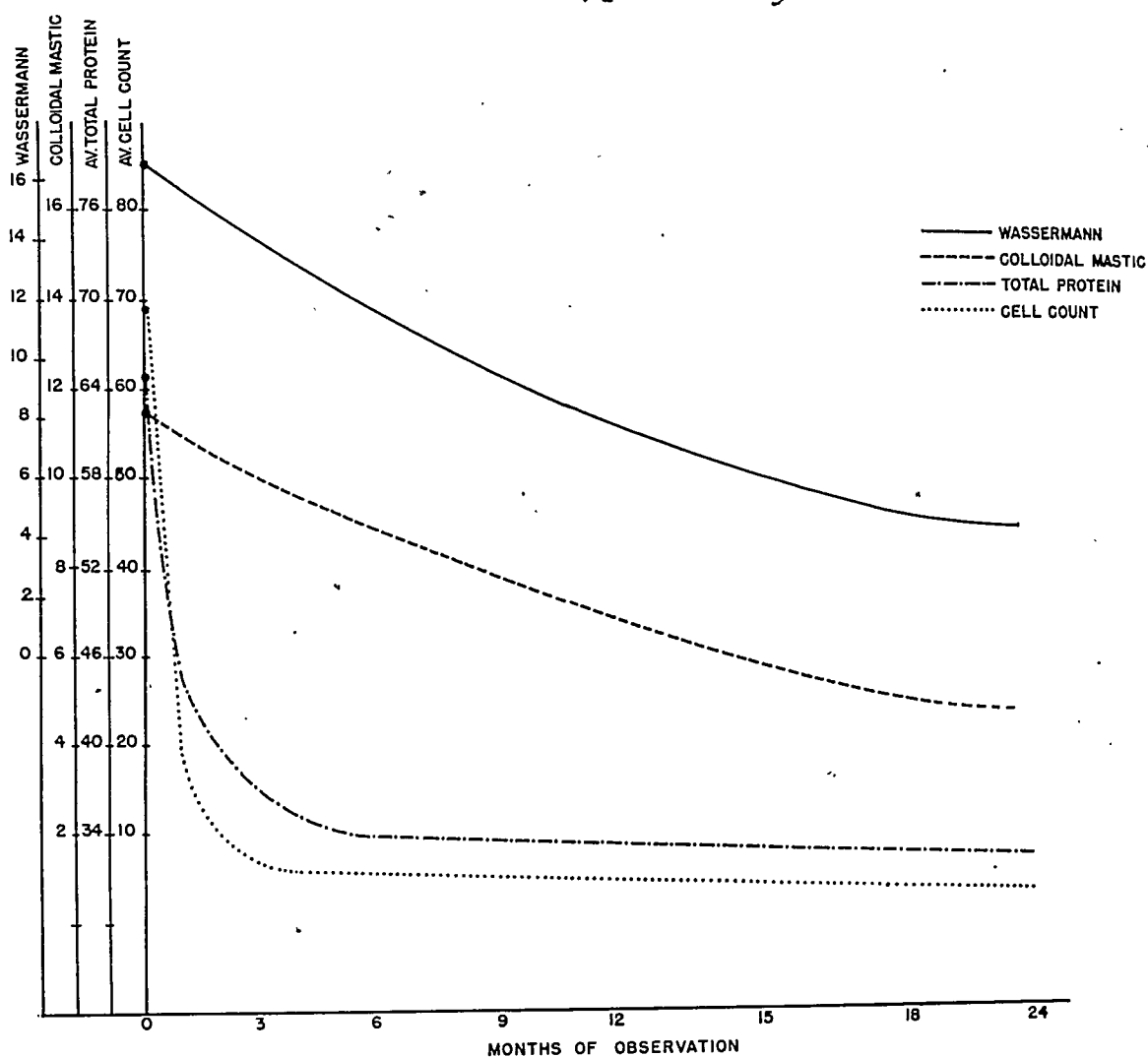


FIG. 2. Changes in spinal fluid abnormalities (all neurosyphilis) following treatment with penicillin alone.

abnormalities of neurosyphilis. This improvement is observed in a high proportion of patients treated, the immediate effect being approximately equally favorable regardless of the type of neurosyphilis.* It has been generally well sustained, at least during the limited period of observation so far available.

The changes in the spinal fluid follow a fairly regular pattern. (Fig. 2.) Elevated cell counts and total protein determinations become normal promptly, usually within a few weeks. This is followed by far more gradual but equally well sustained improvement in the results of colloidal tests and in the Wassermann titer.

Thus, as a result of penicillin therapy the

* With the possible notable exception of Erb's spinal spastic paraplegia.

evidences of "activity" rapidly and almost invariably disappear from the cerebrospinal fluid. Not in all cases, however, does the fluid remain inactive. In the series of patients at the Johns Hopkins Hospital, spinal fluid relapse six or more months after treatment has occurred in approximately 7 per cent of those who have been under observation for at least that period. Reactivation of the spinal fluid has been noted more frequently among those with symptomatic (usually parenchymatous) neurosyphilis (9.4 per cent) than among those with asymptomatic involvement of the neuraxis (4.4 per cent).

Asymptomatic Neurosyphilis. In patients whose only evidence of neurosyphilis is a positive spinal fluid, the results of therapy can be adjudged only by: (1) the post-

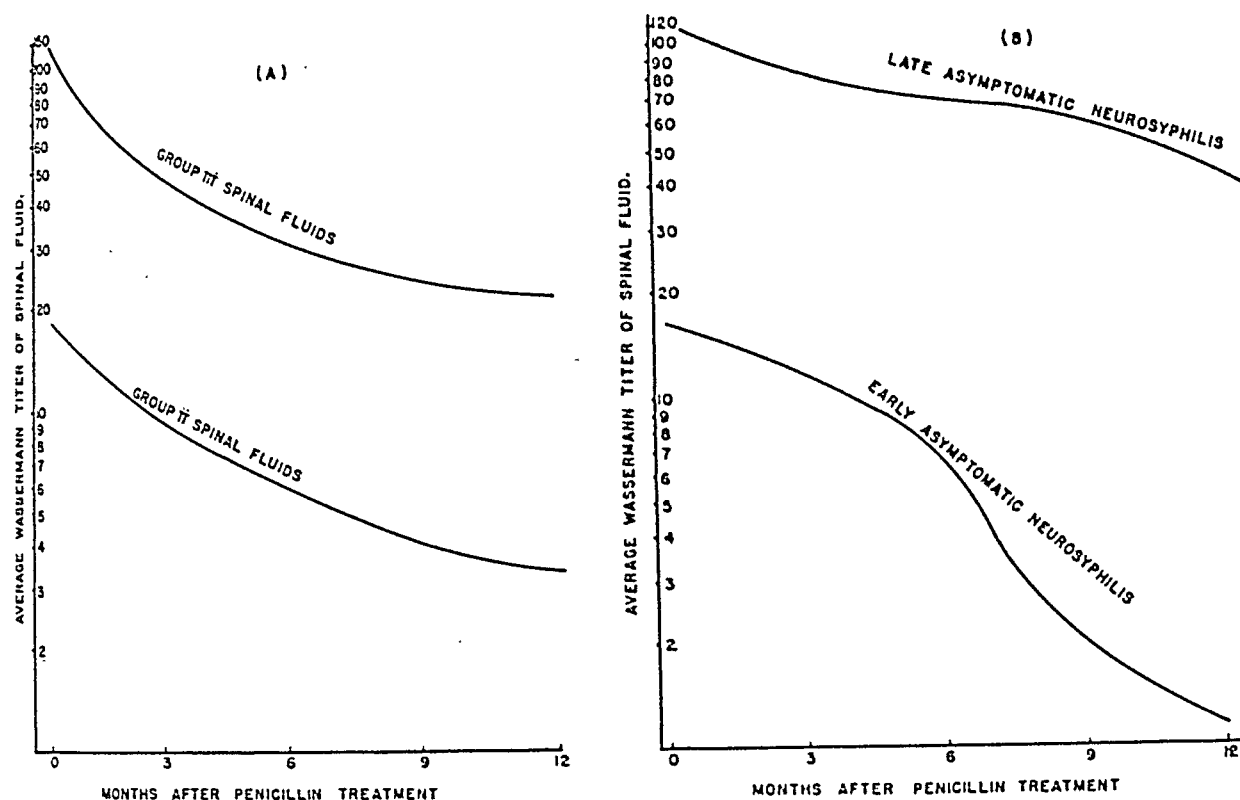


Fig. 3. Average spinal fluid Wassermann titer (arbitrary units)³² following penicillin therapy, to show the influence of; (A) degree of pre-treatment abnormalities and (B) duration of syphilitic infection. JHH data, smoothed curves.

treatment response of the spinal fluid, and (2) the incidence of progression to clinical neurosyphilis.

The early effect of penicillin upon the spinal fluid has been distinctly encouraging. Moore and Mohr,³² who recently summarized this clinic's first two years' experience, believe "... that penicillin exerts a profoundly favorable effect on spinal fluid abnormalities in early and late asymptomatic neurosyphilis; that this is manifest, in order of promptitude and extent, on cell count, protein content, colloidal test, and, last of all, on the complement fixation (Wassermann) reaction. . . . Within the brief time limits of this study [average duration of observation, 9 months], and keeping in mind the small number of cases involved [91], spinal fluid normality, once achieved, seems usually to be stable."

In asymptomatic neurosyphilis, the *rapidity* with which the spinal fluid becomes normal following penicillin therapy is dependent upon two factors: the degree of the pre-treatment abnormalities, and the dura-

tion of the syphilitic infection. (Fig. 3.) Lesser degrees of abnormality and those occurring within the first two years of syphilitic infection disappear rapidly; those more extensive and of longer duration improve slowly over a period of years.

The ultimate result in terms of clinical progression will not be known for many years. If, however, the Dattner-Thomas concept is valid for asymptomatic neurosyphilis, and if the favorable spinal fluid responses thus far noted, sustained, the incidence of clinical neurosyphilis developing in this group of patients should be low.

Effect of Penicillin upon the Clinical Manifestations of Neurosyphilis. However great may be the difficulties in evaluating clinically the results of penicillin therapy in symptomatic neurosyphilis, it is desirable to attempt an over-all approximation. Surely the patient is more interested in how much relief he may expect from his lightning pains or from his mental disturbance than in the cell count of his spinal fluid.

To this end, an attempt has been made to determine from the Johns Hopkins Hospital material what proportion of patients with various forms of neurosyphilis are considered to have been "improved" as a result of penicillin therapy. Details may be found in the several recent reports from this clinic,^{33,34,35,36} which summarize the early experiences with penicillin in various forms of neurosyphilis.

Sufficient material has been studied to make a preliminary estimate of the results of penicillin therapy in tabes dorsalis, and in syphilitic meningitis, general paresis, and Erb's spinal spastic paraplegia. (Table II.)

TABLE II
EARLY RESULTS OF THERAPY WITH PENICILLIN ALONE
IN CERTAIN FORMS OF NEUROSYPHILIS

	Change	
	"Im- proved" Per Cent	No Change or Worse Per Cent
Acute syphilitic meningitis ³³	100	0
Paresis and taboparesis ³⁴	46	54
Tabes dorsalis ³⁵	37	63
Erb's spinal spastic paraplegia ³⁶	0	100

No significant conclusions can yet be drawn in respect to diffuse meningovascular neurosyphilis, syphilitic epilepsy, primary optic atrophy or nerve deafness, although a few patients in each of these categories have been treated.

It is apparent from Table II that the results of penicillin therapy in acute syphilitic meningitis are excellent, but in parenchymatous neurosyphilis the results are not outstandingly favorable. Such improvement as occurred was attained, however, without subjecting the patient to the considerable dangers inherent in fever therapy.*

* In expert hands, the mortality rate from malarial therapy is approximately 1 per cent, from mechanical fever, as high or higher. The percentage of deaths due to fever treatment is inversely proportional to the care used in selecting patients for this rigorous form of therapy and the skill and experience of the attending physician.

There are sound reasons for combining fever with penicillin in the treatment of neurosyphilis. The combination of two effective forms of treatment might be expected to be superior to either alone. Moreover, the spirochicidal activity of penicillin is known³⁷ to be enhanced at fever temperatures.

The concurrent administration of penicillin with malarial fever therapy appears, from the experience with general paresis,³⁴ to offer the patient with late parenchymatous neurosyphilis the greatest promise of a favorable outcome. It is the treatment of choice, therefore, in those forms of neurosyphilis which carry a serious risk to life or vital bodily function: paresis and taboparesis, primary optic atrophy and nerve deafness (in late acquired or congenital syphilis).

For the various syndromes of neurosyphilis, the initial treatment of choice, in the light of information now available, is as shown in Table III.

TABLE III
INITIAL TREATMENT OF CHOICE IN THE VARIOUS SYNDROMES OF NEUROSYPHILIS

PENICILLIN ALONE	
FEVER PLUS PENICILLIN	General paresis and taboparesis
Acute syphilitic meningitis	Early asymptomatic neurosyphilis
Primary optic atrophy	Nerve deafness (in late acquired or congenital syphilis)
LATE ASYMPTOMATIC NEUROSYPHILIS	
Group II	Syphilis
Group III	Diffuse meningovascular neurosyphilis
Group II	Tabes dorsalis
Group III	Erb's spinal spastic paraplegia

The therapeutic problem in tabes dorsalis and in Erb's spinal spastic paraplegia requires further consideration. In each, the outlook ultimately is for distressingly chronic invalidism. Since the evolution of these conditions



FIG. 4. A, gumma of the palate before and B after treatment with penicillin (Dexter and Tucker³⁹).

ditions is gradual, with no immediate threat to life or vital bodily function, and since these patients frequently are in such poor general physical condition as to be poor fever therapy risks, it is not unreasonable first to try a form of therapy (e.g., penicillin) which is completely safe, provided there is any reasonable prospect that such therapy may be beneficial. In *tabes dorsalis* there is such a prospect, but in Erb's spastic paraplegia there appears not to be any.

In any form of neurosyphilis in which penicillin is given as the initial course of treatment, the outcome should be carefully reviewed within six months. If there has been no improvement within that length of time, none may be expected. Re-treatment, usually with malaria (plus penicillin?) may then be indicated, especially if there is evidence of "activity" in the cerebrospinal fluid.

PENICILLIN IN THE TREATMENT OF OTHER MANIFESTATIONS OF SYPHILIS

Benign Late Syphilis. The healing of³⁸ the lesions of benign late syphilis affords a most convincing demonstration of the value of

penicillin in the treatment of syphilis. Dexter and Tucker,³⁹ who have studied twenty-one patients with benign late gummatous syphilis in this clinic, report entirely favorable results. In eighteen cases, cutaneous, mucocutaneous or mucosal gummas were present; four of the patients had osseous lesions, and two, gummas of the liver. In these patients the clinical response was uniformly favorable. Cutaneous and mucosal gummas underwent rapid and progressive improvement (Fig. 4) after penicillin therapy, there being only one incipient relapse and one treatment failure in the entire group. The lesions of both of these two patients healed completely following a second and more intensive course of penicillin. Late syphilitic lesions of the skeleton and of the liver appeared to respond favorably to penicillin.

Cardiovascular Syphilis. Evaluation of usefulness of any therapeutic agent in cardiovascular syphilis involves many years post-treatment observation. There is, therefore, little information as to the results of penicillin in this important late manifesta-

tion of the disease. We have observed in a few patients some amelioration of the presenting symptoms (precordial pain, dyspnea) following treatment with penicillin. How much of this symptomatic improvement may have been due to hospitalization, bed rest and sedation is difficult to assess.

Caution has been urged⁴⁰ in the use of large doses of penicillin in the presence of cardiovascular syphilis in view of possible complications from therapeutic shock. This reaction has not been a serious problem in the limited series of patients coming under our own surveillance.

Latent Syphilis. In the treatment of latent syphilis, the purpose is to prevent the development of late manifestations of the disease. How adequately this can be accomplished with penicillin will not be known for several decades.

The only rationale for treating patients with latent syphilis with penicillin is by analogy. Since the drug possesses spirocheticidal action, and since it promotes the healing of manifest lesions, it is not unreasonable to expect that it *may* avert late complications if given at a time when the infection is clinically latent.

It is obvious, however, that treatment with penicillin offers nothing to those whose serologic test remains positive following adequate⁴¹ metal chemotherapy. To subject this group of patients to further therapy of any kind is to kindle false hopes and to waste time, money and effort.

Early Congenital Syphilis. In infants with congenital syphilis, penicillin appears to be at least as effective* as in early acquired syphilis in adults.^{42,43,44} There obtain the same therapeutic considerations, especially in regard to time-dose relationships, although the total penicillin dosage and the

size of each injection may be reduced in proportion to the body weight.

Infants with early congenital syphilis often are seriously ill. To add to their already precarious condition, therapy which in itself may be toxic, is highly undesirable. To the extent that penicillin is almost completely devoid of untoward reactions (save alone Herxheimer effects, which only occasionally appear to constitute any serious hazard), it is preferable to older forms of therapy.

There is the additional and highly important consideration of proper pediatric care, with especial attention to adequate hydration and nutrition, and the recognition and treatment of intercurrent infections.

Syphilis in Pregnant Women. In the prevention of prenatal syphilis through treatment of pregnant women with syphilis, penicillin has been highly efficacious.⁴⁵ Here it may well be, as Goodwin and Moore⁴⁶ suggest, the therapy of choice.

Penicillin readily passes the placental barrier⁴⁷ and its spirocheticidal action thus is available to the fetus *in utero*. It appears, despite the contention of some,^{48,49} not to provoke uterine contractions and not to precipitate labor.⁴⁹ No abortifacient effect of the drug has been apparent in the group of patients treated in this clinic.

The outlook for a non-syphilitic child following penicillin therapy during pregnancy is excellent. Even among those mothers whose syphilitic infection has been recently acquired, and in whom the risk to the child is great,⁵⁰ there have been remarkably few treatment failures. Because of the possibility of redissemination of organisms in the course of an infectious relapse, frequent post-treatment observations throughout the remainder of pregnancy are imperative.

SUMMARY

In penicillin there is added to the armamentarium of the syphilotherapist a drug

* The incidence of infectious mucocutaneous relapse thus far has been significantly lower in infants with early congenital syphilis than in adults with early acquired syphilis.

which is of negligible toxicity, readily administered, but with definite limitations in therapeutic effectiveness. It is far from being the ideal form of treatment; yet it is more than a fad. It has, for the present at least, a place in the treatment of syphilis as the most desirable form of therapy presently available for certain of the protean manifestations of this disease and as an adjunct to older methods in others.

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Combined Staff Clinics

Rheumatoid Arthritis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. CHARLES RAGAN: We would like to discuss a group of diseases which, while very different in some respects, have certain important characteristics in common. This group includes serum sickness, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, rheumatoid arthritis and scleroderma. It is now the fashion to classify these diseases together as disorders of the mesenchyme because they all show pathological changes in connective tissue, with clinical signs usually centering upon the joints and contiguous tendon sheaths, but with microscopic evidence of changes in muscle tissue, the subendothelial tissue of blood vessels and the endocardium, and the connective tissue of the myocardium.

Clinically, too, there is considerable overlapping. For example, it may be difficult to tell whether a given patient has rheumatic fever, rheumatoid arthritis or lupus erythematosus disseminatus. The following cases illustrate some of these points.

The first patient is Mrs. S. I believe you can all see that she has typical fusiform fingers with some limitation of motion of her wrists. The onset of her disease was fairly acute, in January, 1946. She came to us in June, 1946, after rather ineffective treatment. At that time—in June—she was in a wheelchair, confined to her home with flexion deformities of both elbows and both knees. She had a moderate hypochromic anemia. Her blood showed an elevated sedimentation rate and gave a positive agglutination test with group A hemolytic

streptococci. We wish to show her as a patient with rheumatoid arthritis in a remission. She has been treated with whole blood transfusions, gold and curare. At the present time she has no flexion deformities, she is able to do her own housework and drives a car.

The second patient is Kathie P., who is now nine years old. She has been sick since 1943. In December, 1943, she had a sore throat followed in two weeks by polyarthritis. At the time she was in another hospital where she had definite pericarditis with effusion. She was first seen in the Babies Hospital in June, 1944, by which time she had developed flexion deformities of both wrists and both knees, and had by x-ray loss of joint space in both wrists. Throughout this period she had episodes of fever up to 105°F., which sometimes responded to salicylates and sometimes did not. In 1945 and 1946, she was in the hospital on three or four occasions and at the present time the disease process is still active, with an elevated sedimentation rate and some flexion deformities.

Kathie is to us an example of what is called Still's disease, which is essentially rheumatoid arthritis in childhood. In this age group you see the greatest interrelation between rheumatic fever and rheumatoid arthritis.

The third patient recently came to autopsy. In 1936, two weeks after delivery, she developed polyarthritis with pericarditis. In 1936, 1937, 1938 and 1939, she was

seen at various times at another hospital with episodes of fever. She had several attacks of pleurisy and two bouts of pneumonia. In 1939, while in the hospital, she was observed to have a definite "butterfly" rash on the face. In 1941, she developed ankylosis of the wrists with persistent joint pain and subluxations of the proximal phalangeal joints. In 1943 and 1944, she received some chrysotherapy at the Presbyterian Hospital, and in 1945 she received Bogomolets' serum, all without benefit. In 1946, she was given adequate chrysotherapy, again with no improvement, and she was transfused with whole blood. In August, 1946, she was admitted to Presbyterian Hospital in cholemia and died. I have a picture of her showing the "butterfly" rash. Another picture shows her hands, which are as characteristic of rheumatoid arthritis as any we have seen. A biopsy of the gastrocnemius muscle in 1945 showed a small perineural lymphocytic nodule and at autopsy the characteristic lesions of lupus erythematosus disseminatus were found to be widespread.

These cases illustrate the clinical and pathological overlapping in the diseases which we would like to consider as a group. We are not clear about the pathogenesis of any of these diseases. Most of the work done in this field in the past has been in the nature of clinical classification. Today we are not concerned so much with classification as with an attempt to clarify the common denominator of the whole group, namely, the pathological lesion located in the mesenchymal or connective tissue.

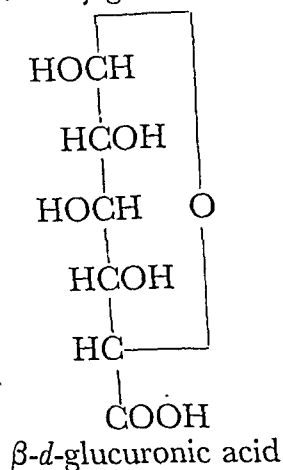
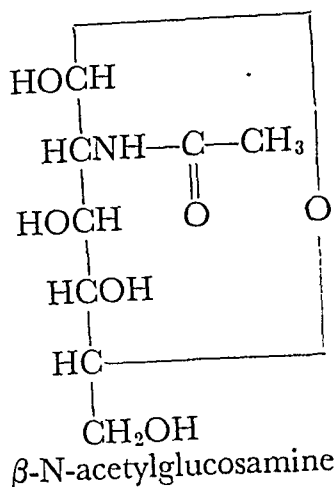
We might begin our discussion with a summary of recent progress in the chemistry of connective tissue. Dr. Karl Meyer, who has contributed so much to our understanding of the mucopolysaccharides and mucoproteins, is here to present this phase of the subject.

DR. KARL MEYER: Connective tissue is

composed of two major structural components, the fibrous elements and the cement substances. The two components belong to quite different classes of chemical substances, the fibrous elements being denatured, insoluble, fibrous proteins of very high molecular weight; whereas the cement substances are compounds or complexes of protein with highly polymerized mucopolysaccharide acids.

The fibrous elements fall into three main groups histologically: collagenous fibers, reticulin fibers and elastic fibers. Collagenous and reticulin fibers are said to be identical in origin and probably have the same chemical structure. The differentiating feature of the two, namely, the silver impregnation of the reticulin fibers, is attributed to closer packing of the fibrils but may, however, be due to a higher concentration of strongly reducing groups in the polysaccharides of the cement substances, as compared with collagen fibers. Collagen and elastic fibers both have a high glycine and proline content but differ in their content of other amino acids. Study by x-ray and electron microscopy of collagen fibers in tendon, loose connective tissue, skin and cornea has revealed a fine crystalline structure of the constituent fibrils; with alternating bands of higher and lower density spaced at regular distances from each other. By heating in aqueous solution, the crystalline collagen is converted into soluble and amorphous gelatin. Rat-tail tendon and all embryonic collagen fibers are soluble in salt-free dilute acids, forming extremely viscous solutions, as Nageotte has shown; while all other collagen fibers are insoluble in these solvents. The cause of this difference in solubility is unknown. On addition of salt or on neutralization, the proteins in these solutions precipitate as fibers which possess the same fine structure as the native fibers. Native adult collagen fibers are digested by pro-

teolytic enzymes at a very low rate, comparable to the digestion of other fibrous proteins, like keratin.



The interfibrillar or cement substances seem to be of considerable importance in the mechanism of rheumatic diseases, and will be discussed in some detail. According to the fundamental studies of Klinge, the primary lesions in rheumatic fever and rheumatoid arthritis are located in the interfibrillar spaces, while the swelling, fragmentation and finally lysis of the fibers is a secondary phenomenon. The chemical nature of the proteins of the cement substances is unknown. The mucopolysaccharides which are more or less loosely bound to the proteins have been studied more extensively. Up to the present time four mucopolysaccharides have been identified as components of cement substances, (1) hyaluronic acid, (2) hyaluronosulfuric acid, which has been found only in cornea,

(3) chondroitin sulfuric acid, and (4) the sulfuric acid ester occurring in amyloid tissue. The latter may be a component of normal mesodermal tissue which accumulates in excessive amounts in amyloid disease. It appears to be derived from heparin.

Hyaluronic acid is a polymer of a disaccharide composed of N-acetyl glucosamine and glucuronic acid. Its exact structure, like that of other mucopolysaccharide acids, is still unknown. The molecular weight of hyaluronic acid varies according to the source from which it is obtained; it has been estimated as between 200,000 and 500,000, and may be even higher. Hyaluronic acid occurs in vitreous and aqueous humor, in Wharton's jelly of umbilical cord, in synovial fluid, in skin and in some mesodermal tumors. In micro-organisms, it has been found only in group A and C hemolytic streptococci, when the organisms are in the mucoid phase. Mucoid phase and hyaluronate production have been correlated in some types with invasiveness of the organisms and with their resistance to phagocytosis and to destruction by whole blood. All attempts to produce antibodies against hyaluronic acid have failed.

Hyaluronic acid is depolymerized and hydrolyzed by specific enzymes called hyaluronidases, which occur in micro-organisms such as pneumococci, streptococci, staphylococci and in gas gangrene-producing organisms. Among animal sources the enzyme has been found in snake venoms, in the leech, and (in very high concentration) in the mature mammalian testis, or, more specifically, in spermatozoa. In the latter, the enzyme facilitates the depolymerization of the mucoid ground substance of the cumulus cells of the ovum, thus preparing it for fertilization. The greatest store of hyaluronidase in the mammalian body seems to be the skin where, however, it appears to be largely in an inactive form.

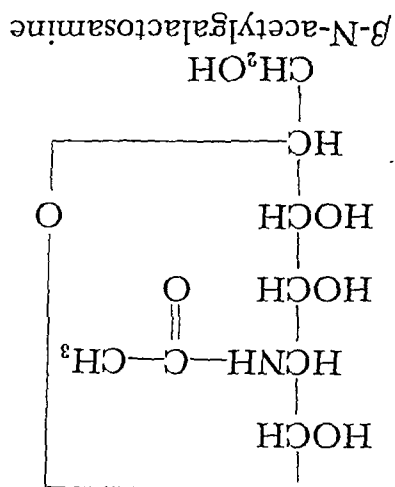
hyaluronate, while cartilage contains only chondroitin sulfate.

Chondroitin sulfates probably are mixtures of similar but not identical compounds, some of which are hydrolyzed by hyaluronidases or by enzymes associated with hyaluronidases. The spreading effect in some tissues thus may be due to the hydrolysis of chondroitin sulfate rather than to that of hyaluronate. The metachromasia of some dyes (such as toluidine blue) shown by connective tissue and cartilage appears to be caused by chondroitin sulfate. Hyaluronate does not seem to be stained by any of the usual methods.

The known data of the chemistry of the connective tissue, when considered in relation to what has been learned by histological and tissue culture studies, suggest the following mechanisms in the development of connective tissue: The young, growing fibroblasts secrete hyaluronic acid, which is followed by the secretion of chondroitin sulfate and of a precursor of collagen, the latter a non-fibrous and soluble protein. By local acidification in the immediate neighborhood of the fibroblasts, the precursor is denatured by the polysaccharides, the latter acting as anionic detergents rolling up the peptide chains along the acidic groups of the fibrous polysaccharide molecules. Most of the hyaluronate is removed enzymatically, leaving the more firmly bound chondroitin sulfates as a network on the surface of the fibers. The latter by crosslinking grows into the mature insoluble

The pathological chemistry of connective tissue is still in an embryonal state. However, some insight into this field might be gained by recent studies (in collaboration with Dr. Ragan) on synovial fluid which embryologically, and to some extent physiologically, is related to connective tissue. The concentration of hyaluronate was measured by a turbidimetric method in

A very interesting property of hyaluronidases is their effect on dermal diffusion, the so-called spreading reaction of Duran-Reynals. This reaction usually is carried out in rabbits or in guinea pigs, but also has been observed in man. On intradermal injection of an indicator together with suitable concentrations of enzyme, the indicator diffuses in the skin over a wide area as compared to the localized bleb in control injections of indicator without hyaluronidase. The spreading reaction has been demonstrated also in the wall of the stomach and intestine, in muscle, fasciae and tendon. However, in contrast to skin, no hyaluronic acid has been isolated thus far from these sources.



Chondroitin sulfuric acid has a molecular weight similar to that of hyaluronic acid. It is a polymer of a disaccharide composed of equimolar concentrations of N-acetylglactosamine, glucuronic acid and sulfuric acid, the latter apparently in the C₆ position of the galactosamine. Chondroitin sulfuric acid has been isolated from hyaline cartilage, from umbilical cord and from skin. A fraction recently isolated from calves' tendon is probably also chondroitin sulfate. It should be noted that two tissues contain hyaluronate and chondroitin sulfate in about equal concentrations, namely, skin and umbilical cord. Synovial fluid, vitreous humor and the tumor fluids contain only

normal and pathological synovial fluids. Pathological fluids in this reaction appear as a stable colloidal turbidity, while normal fluids of man and cattle precipitate as a fibrous clot containing the polysaccharide. This clot formation is prevented by one hundredth of a unit of hyaluronidase, an amount too small to decrease measurably the hyaluronate concentration. With normal vitreous humor a colloidal precipitate is obtained, while in aqueous humor 95 per cent of the total hyaluronate is found in depolymerized, non-precipitable form. This depolymerization is due to the co-presence of hyaluronidase, which was demonstrated in a concentration of about 0.4 u/cc. in ocular fluid.

In synovial fluid no measurable amount of hyaluronidase could be demonstrated, unless the colloidal precipitation is taken as an indication of the presence of the enzyme in low concentration. The viscosities of over thirty synovial fluids examined were not directly proportional to the hyaluronate concentrations, the viscosities being higher and the hyaluronate concentrations lower in normal fluids as compared with pathological synovial fluids, obtained chiefly from cases of rheumatoid arthritis. In view of the increased volume of fluid in these pathological joints, they contain a considerably larger total amount of hyaluronic acid. In other words, the injured synovial cells apparently produce an excess of the acid, which may be followed by a compensatory increase of hyaluronidase, the source of which is undetermined.

Similar changes may occur in other mesenchymal tissue spaces leading to an increase in interfibrillar cement substances. Such an increased concentration of highly viscous material would presumably slow down metabolic processes.

DR. RALPH H. BOOTS: What is the relation of "mucin" and "mucinae" to hyaluronic acid and hyaluronidase?

DR. MEYER: The term "mucin" in classical usage means any viscous secretion which on acidification with dilute acetic acid gives a ropy precipitate. Synovial fluid, which contains hyaluronic acid in considerable concentration, shows this phenomenon and is therefore said to contain "mucin." However, the "mucin" precipitated in this way is an artefact since the native hyaluronate of synovial fluid is not bound to protein, as shown by electrophoretic studies. Vitreous humor and some cystic tumor fluids also contain hyaluronic acid but often fail to give a precipitate with acid. The low protein or high salt content of these fluids is responsible for their failure to precipitate. Gastric mucin contains two mucopolysaccharides which are unrelated to hyaluronic acid. Salivary mucin, too, contains no hyaluronic acid.

The term "mucinae" has also been used to denote different enzymatic reactions, such as depolymerization of the mucopolysaccharide of synovial fluid (hyaluronic acid), the liquefaction of salivary mucus, etc.

I think it would be best either to drop the ambiguous terms "mucin" and "mucinae" or to use them only in a non-chemical sense.

STUDENT: Vitamin C has been shown by Wolbach to be essential for the growth of connective tissue. How does vitamin C fit into your concept of connective tissue development?

DR. MEYER: There is no definite information on the rôle of ascorbic acid in the genesis of the fiber. The sensitivity of some of the chondroitin sulfates to alkali and oxygen, and their ultraviolet spectra, suggest that ascorbic acid or a derivative of it may actually be a component of chondroitin sulfate, perhaps replacing some of the glucuronic acid units.

DR. RAGAN: We now would like to turn to one of the group, rheumatoid arthritis.

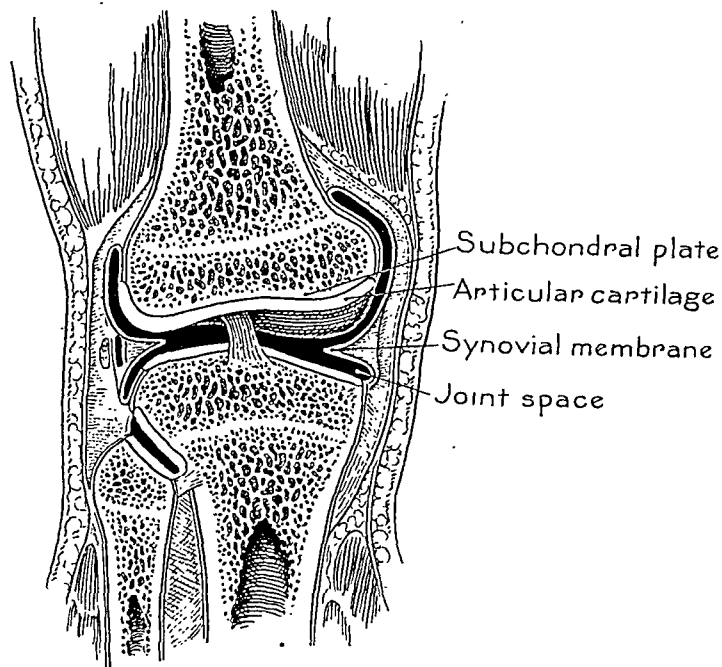


DIAGRAM OF DIARTHRODIAL JOINT

FIG. 1.—(After Callender.)

This is a severe progressive disease. It is of great social and economic import and various public health surveys have shown that chronic arthritis is a major cause of suffering and economic loss. Until recently rheumatoid arthritis was considered a disease purely of the joints. In the past ten years, however, evidence has accumulated which indicates that the disease is more generalized. Dr. Flynn of the Department of Pathology has been asked to discuss the morphological changes which are found.

DR. JOSEPH F. FLYNN: As has been stressed by previous workers, rheumatoid arthritis is indeed a protean disease, a disease whose clinical course may be characterized by remissions and exacerbations, a disease whose onset may be acute or insidious, a disease which may attack the individual at any age, a disease which may progress with incredible rapidity producing what has been aptly called the rheumatoid derelict, or again a disease which after a brief course may end abruptly, disappear and never return again.

The systemic pathology of this disease is almost as varied as are its clinical manifestations. By "systemic pathology" I mean the

lesions of the kidney, the bladder, the lymph nodes, the eye, etc. There are, however, a number of locations in which the changes are remarkably constant and it is on these that I will chiefly dwell. These locations are the joints, the nodules of the subcutaneous tissue, the nerves and the muscles.

Joint Pathology. Before demonstrating the pathology of the rheumatoid joint, I will review very briefly the anatomy of the diarthrodial joint. The anatomy of diarthrodial joints is essentially the same regardless of their location, whether the hand, wrist, foot, shoulder, knee, etc. The bones constituting the joint are covered by a layer of hyaline cartilage, called the articular cartilage. (Fig. 1.) It rests on a thin layer of dense bone known as the subchondral plate. You will recall that the joint cavity is lined by a continuous membrane, the stratum synoviale or the synovial membrane. This is a layer of specialized connective tissue. It begins at the margin of the articular cartilage, covers the intra-articular portions of the bones and is reflected on the capsule to end at the margin of the opposite articular cartilage. Microscopically, the surface of the synovial membrane is thrown up into a number of tiny villous projections. This gives the membrane great flexibility, permitting it to be stretched for a considerable distance.

The synovial membrane is made up of collagen in which are imbedded the synovial cells—the modified fibroblasts. Intermixed with connective tissue, are a number of blood vessels, a few lymphatics, a few nerves and a few wandering cells. The structure of synovial membrane is essentially the same regardless of its location. However, the tissue on which it rests may vary.

The primary lesion of rheumatoid arthritis is an inflammation of the synovial membrane. It becomes enormously thickened by edema, hyperemia and inflammatory cell infiltration. As a result of



FIG. 2. Subacute villous synovitis from a case of severe rheumatoid arthritis. The stratum synoviale is enormously widened by edema, hyperemia and inflammatory cell infiltration.

edema there is often seepage of fluid out into the joint and this together with the increased activity of the synovial cells accounts for the great increase in joint fluid. This increased joint fluid stretches the capsule, often producing pain.

Figure 2 shows the rather typical appearance of the inflamed synovial membrane. Note the enormous widening of the membrane and the exaggeration of the villous projections. In the hypertrophic villi are collections of lymphoid cells. Some years ago an orthopedist, describing the pathology of rheumatoid arthritis, found collections of lymphocytes so arresting that he stated they were absolutely specific for rheumatoid arthritis. This is but another example of the all too frequent attempt to create pathological specificity on the basis of insignificant morphological alterations. Needless to say, there is nothing pathognomonic about it. They are found in a number of conditions.



FIG. 3. Subacute villous synovitis with pedunculation of one of the villi. Often these pedunculated villi become necrotic and separate away to form free bodies within the joint. Note the increased vascularity, widening of the tissue spaces and inflammatory cell infiltration.

Often in rheumatoid arthritis the hypertrophic villi become pedunculated as seen in Figure 3. If these pedunculated villi become necrotic, they separate away to form free bodies in the joint space. Large amounts of fibrin are often deposited on the surface of the membrane or in the membrane itself. The fibrin is eventually organized and adhesions may result. In severe cases the inflamed synovial membrane may project into the joint space to form a pannus that creeps across the cartilage, like ivy grows across a wall. As it creeps across, the articular cartilage is destroyed. Now, and now only, excluding osteoporosis and swelling of the soft tissue, does roentgenographic evidence become apparent. This evidence consists first of a narrowing of the joint space due to disintegration of the articular cartilage. In severe cases, often simultaneously with the formation of the pannus, granulation tissue forms just beneath the subchondral plate.

Figure 4 is a section through the distal end of a normal femur. It shows a portion of the articular cartilage, beneath which is the subchondral plate. Below the subchondral plate are narrow spaces normally occupied by fibro-fatty tissue. In severe rheumatoid arthritis granulation tissue is present in the marrow spaces just beneath



Fig. 4. A section through the distal end of a normal femur. Above is a portion of the articular cartilage, resting on a layer of compact bone called the subchondral plate. Below is the fibro-fatty marrow.

the subchondral plate. The proliferation of the granulation tissue destroys the osseous trabeculae and the subchondral plate. When this occurs the articular cartilage is attacked from above and below, above by the pannus and below by the granulation tissue. If this occurs in both bones, the end result is a bridge of granulation tissue that stretches across the joint space. In time the granulation tissue becomes converted into fibrous tissue, producing a fibrous ankylosis. Figure 5 shows some of these changes. The articular cartilage is degenerated as manifested by its altered staining reaction, the disalignment of the cells and empty lacunae. Above the articular cartilage is a pannus. Below the articular cartilage there is dissolution of the subchondral plate. Near one margin the granulation tissue from below almost reaches the pannus.

Figure 6 is a section from a "burned-out"



Fig. 5. A photomicrograph of a section through a diarthrodial joint showing marked rheumatoid arthritic changes. Above is the pannus creeping across the articular cartilage. The cartilage is degenerating. Note its altered staining reaction of the cartilage, large lacunae and disorderly arrangement of the cells. Below the articular cartilage, granulation tissue has destroyed the subchondral plate and is replacing the cartilage.

case of rheumatoid arthritis. This patient had an ankylosis of the femur and tibia. Here there is complete destruction of the articular cartilage with replacement by dense connective tissue.

Figure 7 is a roentgenogram of a wrist joint showing severe rheumatoid arthritic changes. Note that the joint spaces of the metacarpals are destroyed. The joint spaces between the metacarpals, radius and ulna are bridged across by osseous tissue. It must be remembered that the entire sequence of events just enumerated does not always occur. In many cases the process simmers along with remissions and exacerbations, without much pannus formation and without much granulation tissue beneath the subchondral plate.

Subcutaneous Nodules. As Bennett and Bauer¹ point out, the nodules of the subcutaneous tissue have received a great deal of attention. These workers have stressed the point that they are probably the most

¹ BENNETT, G. A., ZELLER, J. W. and BAUER, W. Subcutaneous nodules of rheumatoid arthritis and rheumatic fever; pathologic study. *Arch. Path.,* 30: 70-89, 1940.



FIG. 6. A photomicrograph showing the end state of rheumatoid arthritis—fibrous ankylosis. Above is dense connective tissue. The articular cartilage is destroyed as is the subchondral plate. The granulation tissue has disappeared and the marrow spaces are occupied by fibro-fatty tissue.

specific lesion of rheumatoid arthritis. The nodules usually measure about 1 to 2 cm. in size. Basically they consist of connective tissue in which are a number of granulomatous lesions. As a rule there are about five granulomatous lesions in the plane of any given section studied. The granulomas are made up of a zone of necrosis, then a zone of inflammatory cell reaction and then a zone of connective tissue. The necrotic tissue is disintegrated collagen. The inflammatory reaction consists of large mononuclear cells. Often multinucleated giant cells are present so that the lesion resembles tuberculosis. Indeed these nodules are sometimes called tuberculosis by the misinformed.

Muscles and Nerves. In 1942, Freund²

² FREUND, H. A., STEINER, G., LEICHTENTRITT, B. and PRICE, A. E. Peripheral nerve in chronic atrophic arthritis. *Am. J. Path.*, 18: 865-893, 1942.



FIG. 7. A roentgenogram of the right hand and forearm showing marked rheumatoid arthritic changes. There is reduction of the joint spaces of the wrist and hand due to destruction of the articular cartilage. A bony ankylosis of the carpal bones has occurred involving all except the pisiform. Punched out areas of periarticular bone destruction are present in the distal end of the metacarpal bones. These are due to proliferating granulation tissue beneath the subchondral plate. There is marked ulnar deviation of the phalanges.

and his associates described what they called a specific, inflammatory nodule involving the perineurium of many nerves in rheumatoid arthritis. In 1945, Freund³ described similar lesions in the muscles. He called the lesions in the nerves "nodular perineuritis," and in the muscles "poly-nodular polymyositis."

Figure 8 shows a fairly typical lesion in the perineurium of a nerve, cut longitudinally. Basically the nodule consists primarily of lymphocytes. They may be small, consisting of only a few lymphocytes, or they may be large enough to be seen with the

³ FREUND, H. A., STEINER, G., LEICHTENTRITT, B. and PRICE, A. E. Nodular polymyositis in rheumatoid arthritis. *Science*, 101: 202-203, 1945.

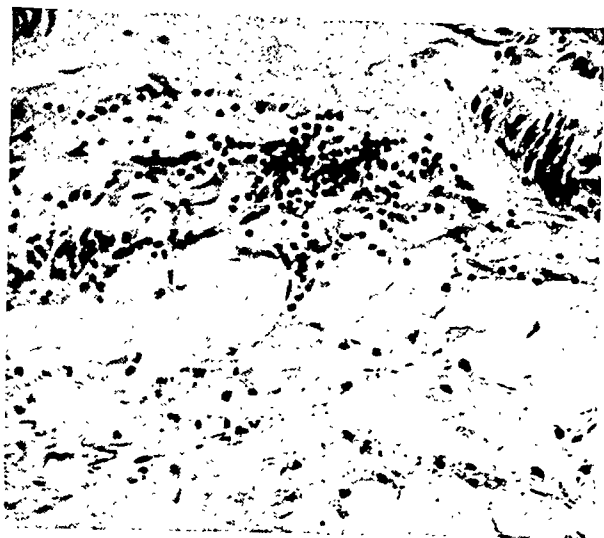


FIG. 8. A photomicrograph showing a nodular perineuritis. Near the top of the photomicrograph is a small nerve cut longitudinally. In the nerve is a dense collection of lymphocytes.

naked eye. Similar lesions⁴ are found in disseminated lupus and in dermatomyositis. Neither are the lesions in the muscles specific, since I have seen identical lesions in the atrophic muscles of poliomyelitis.

DR. RAGAN: The etiology of rheumatoid arthritis is unknown. I have asked Dr. Coss to review the present status of our knowledge of the relation of the hemolytic streptococcus to rheumatoid arthritis.

DR. JAMES A. COSS: Various organisms have at one time or another been implicated as the etiologic agent in this group of diseases without confirmation. At the turn of the century Westphal in Germany, and Poynton and Paine in England, directed attention to streptococci as a result of their cultural studies. This interest has been revived periodically by reports, from abroad as well as in this country, to the effect that a definite organism could be isolated from rheumatic lesions. Up to the present time numerous investigators have been unable to confirm these various reports. No one has succeeded in fulfilling Koch's postulates for any etiologic agent reported associated with rheumatoid arthritis.

Certain bits of evidence have served further to implicate the hemolytic strepto-

coccus, however. Todd has described an antistreptolysin test by means of which the titer of this streptococcus antibody can be measured. For practical purposes it is the antistreptolysin-O which is determined. It is elevated following acute hemolytic streptococcus infections, in nephritis, rheumatic fever and occasionally in the early stages of rheumatoid arthritis.

Cecil, Nichols and Stainsby described an agglutination reaction with group A hemolytic streptococci which was found to be positive in a high percentage of patients with rheumatoid arthritis. This was confirmed in our laboratory by Dawson, Olmstead and Boots. Since 1931, we have tested approximately 10,000 blood specimens for streptococcus agglutination. Fifty to 60 per cent of patients with rheumatoid arthritis give a positive streptococcus agglutination test. We have found a positive agglutination in fifty-six patients with diseases other than rheumatoid arthritis. Of these so-called "false" positives, twenty were in the group of the mesenchymal diseases.

In a review of fifty-six cases of juvenile rheumatoid arthritis⁵ we have found the median antistreptolysin-O titer to be 1 to 250, much higher than the normal maximum of 1 to 100 as read in our laboratory. Of all these patients tested, only three had a positive agglutination with group A hemolytic streptococci, as compared with a figure of 55 per cent positive in the adult disease. The absolute significance of such observations as these cannot be estimated until we know more about the agglutination reaction itself. It has recently been shown that the serum of some patients will agglutinate not only group A hemolytic streptococci but also non-specific particulate suspensions, such as unsensitized collodion particles (Wallis⁶). We are trying to clarify some of these points at present.

⁵ Coss, J. A. and Boots, R. H. Juvenile rheumatoid arthritis. *J. Pediat.*, 29: 143, 1946.

⁶ WALLIS, A. D. Personal communication.

⁴ BAUER, W. Personal communication.

The streptococcus agglutination reaction probably is a non-specific test which, in our laboratory, has proven a useful tool in the study of arthritis. At times it fails to give a positive result in obvious cases of rheumatoid arthritis, very infrequently it gives false positive results, and the mechanism of the reaction is not clear.

STUDENT: Can rheumatoid arthritis be produced in experimental animals by injection of streptococci?

DR. COSS: Much of the difficulty in studying rheumatic disease has been our failure to reproduce the disorder in experimental animals. Streptococci injected intravenously into rabbits will cause arthritis, myocarditis and endocarditis; however, the lesions are not similar to the lesions seen in human beings. Such arthritis is not migratory, does not recrudescence spontaneously and is not self-perpetuating. In the cardiac lesions many similarities exist, but Aschoff bodies have not been described.

Rothbard produced arthritis in forty-five of fifty-one rats by injection of group A hemolytic streptococci from a case of septicemia and Rigdon was able to produce arthritis in rabbits by intra-articular injection of a staphylococcus toxin. None of these experiments, however, has resulted in an arthritis characteristic of the clinical picture as seen in human beings. Selye⁷ produced polyarthritis by treatment with adrenal cortical hormone but the technics necessary to bring about the lesions were quite vigorous.

Spontaneous arthritis has been observed in various animals, notably a polyarthritis of rats first reported and studied by Collier⁸ and assumed to be due to a pleuropneumonia organism; also arthritis in swine due

to the erysipelothrix (Collins and Goldie⁹), "strangles" in horses, and quite recently an arthritis in swine which seems to be caused by a virus (McNutt¹⁰). In these instances, and in many others which might be mentioned, it is possible to find as an exciting factor either an infectious agent or a deficiency in some food element, such as exists in the manganese deficiency sometimes responsible for lameness in swine.

DOCTOR: Since you include serum sickness, which has a well established allergic basis, as one of the group, is there any evidence that any of the others in the group has an allergic basis?

DR. COSS: It has been known for years that administration of heterologous serum in small amounts causes arthritis in 10 per cent of the recipients while large amounts cause arthritis in 90 per cent. It is possible to prevent or markedly diminish the arthritic component of serum sickness by the use of salicylates, and this is the one measure which also seems to benefit most victims of the rheumatic diseases.

Because of the implied allergic nature of one end of the spectrum of rheumatic disease (serum sickness), there has been much interest in the report of Klinge (1940) that it was possible to cause arthritis in rabbits by the repeated injection of horse serum. Rich¹¹ has reported that he was able to cause the lesions of periarteritis nodosa in rabbits also by the injection of horse serum.

Zinsser believed that acute rheumatic fever represented an allergic state for the following reasons: (1) the joint symptoms in anaphylaxis are more or less similar to those seen in articular rheumatism; (2)

⁹ COLLINS, D. H. and GOLDIE, W. Observations on polyarthritis and on experimental erysipelothrix infection of swine. *J. Path. & Bact.*, 1: 323, 1940.

¹⁰ McNUTT, S. H., LEITH, T. S. and UNDERBERG, G. K. An active agent isolated from hogs affected with arthritis. *Am. J. Vet. Research*, 6: 247, 1945.

¹¹ RICH, A. R. Hypersensitivity in pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. of Chicago*, 15: 270, 1945.

⁷ SELYE, H. Hormonal production of arthritis. *J. A. M. A.*, 124: 201, 1944.

⁸ COLLIER, W. A. and STAVERMAN, G. J. The spontaneous polyarthritis of rats and the syndrome induced by inoculation of human material in these animals. *Ann. Rheumat. Dis.*, 2: 58, 1940.

joint fluid cultures in articular rheumatism are usually sterile; (3) the joint lesions caused by injection of bacteria intravenously into animals are usually sterile; and (4) the sensitiveness of joints in experimental animals seems to some extent to run parallel to general sensitiveness. Against the theory of bacterial allergy in rheumatoid arthritis is the fact that no constant relation has been demonstrated between the organisms found and the skin reactions which the organisms in question afford. The sensitivity of the arthritic patients' skin to the nucleoprotein of strains of streptococci does not follow the course of the disease in all cases. Attempts at patient desensitization have failed. The following criteria of an allergic disease have not been fulfilled, namely, the determination of allergen by skin test or passive transfer of sensitivity, the disappearance of symptoms when the allergen is removed, the reappearance of symptoms on re-exposure to the allergen. If we try to enroll the hemolytic streptococcus as a bacterial allergen causing rheumatoid arthritis, it fails to fulfill the second criterion offered. We gave penicillin over a six months' period to ten arthritic patients in doses large enough to inhibit the hemolytic streptococcus but no change occurred in the course of the disease nor was there a change in the streptococcus agglutination reaction from positive to negative.¹² Similar attempts to eliminate the streptococcus by means of sulfonamides have failed in arthritis.

The Caveltis¹³ recently have prepared an antigen from ground-up human heart suspension which was used to coat collodion particles prepared according to the method of Cannon.¹⁴ A positive streptococcus agglu-

¹² COSS, J. A., BOOTS, R. H. and LIPMAN, M. O. Prolonged administration of penicillin in arthritis. (In press.)

¹³ CAVELTI, P. A. Auto antibodies in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 379, 1945.

¹⁴ CANNON, P. R. and MARSHALL, C. E. An improved serological method for the determination of precipitative titers of antisera. *J. Immunol.*, 38: 365, 1940.

tion response with the sera of approximately 75 per cent of rheumatic fever patients was found when tested against this antigen. They previously demonstrated that auto-antibodies to kidney can be produced by immunization of animals with mixtures of group A hemolytic streptococci and kidney of the same species. This work has not as yet been confirmed, but in view of the close relationship of streptococcal infection and rheumatic fever, we are naturally much interested.

DOCTOR: What has been your experience with Bogomolets's serum in the treatment of arthritis?

DR. COSS: The anti-reticular cytotoxic serum, or ACS, which was developed in Russia was said to be of value in the treatment of various conditions including rheumatoid arthritis. Bach¹⁵ treated a group of patients without any appreciable benefit whereupon the originators of the serum said it was of value only in the second or allergic phase of disease. We have treated about thirty patients with this preparation with inconclusive results to date.

DR. RAGAN: It is often difficult to state confidently that such-and-such a patient does have rheumatoid arthritis. To us in the management of the patient, the most important practical problem in diagnosis is to differentiate whether the patient has rheumatoid arthritis or rheumatic fever. The joint symptoms of rheumatic fever are amenable to relatively simple treatment and rarely lead to deformity, whereas the joint manifestations of rheumatoid arthritis are, by and large, progressive and treatment should be so directed that progression is blocked and the deformities which lead to eventual crippling be kept at a minimum.

I would like to mention briefly the use of gold compounds. Gold compounds containing a sulfhydryl group were first used

¹⁵ BACH, F. ACS serum in rheumatism. *Ann. Rheumat. Dis.*, 4: 62, 1945.

in the treatment of rheumatoid arthritis in 1927, by Feldt in Germany. Forestier in France used gold extensively but it was not employed in this country until about 1938.

The treatment is purely empirical. The hypotheses upon which Forestier and Feldt based their rationale for treatment have not been substantiated. Much hostility has been raised towards gold because of the severe toxic reactions which are observed following its use.

Between 5 and 10 per cent of the patients with rheumatoid arthritis are unable to tolerate therapeutic amounts of gold because these patients develop a toxic reaction before an adequate amount of gold can be given. Of patients who have received full treatment, an average of 10 to 20 per cent show no improvement, 40 to 60 per cent show striking improvement with one or two courses. Follow-up studies reveal that at least 80 or 90 per cent of these patients relapse within five years, so that the response to gold constitutes a remission of the disease and not a cure.

It might be worth while to say that the relapse is not as severe as the original disease but, again, the response to treatment with gold after relapse is not as dramatic as the response to the first course.

I want to mention again what Dr. Flynn has stressed, namely, that this is a disease in which spontaneous remissions and exacerbations occur, and any form of therapy must be evaluated critically. However, in the experience of the Arthritis Clinic over a period of seventeen years, in which about 2,000 patients with rheumatoid arthritis have been seen, we have not found any therapy other than gold therapy which will consistently and in a high percentage of cases change the course of the disease. Since we believe that a relapse after gold therapy is to be expected, when a patient shows improvement and no toxicity it is our

present policy to continue administration of gold on a maintenance schedule.

Gold toxicity affects certain systems: the skin, as manifested by various pruritic lesions, with occasional severe exfoliative rashes; the gastrointestinal tract, with stomatitis or abdominal symptoms; and damage to the hemopoietic and renal systems. The stomatitis and renal damage may be due to overdosage, since these are similar to what is found in bismuth and other heavy metal poisoning, and we believe we can avoid these by smaller doses. The dermatitis cannot be predicted in any way. We do not know when to expect it. It may come early and it may come three to four months after the last gold has been given.

There is some encouragement in the use of BAL (British AntiLewsite) in the early treatment of toxicity but at the present time it is too early to evaluate these results. We can say definitely that with the administration of BAL there is a significant increase in excretion of gold in the urine.

The dosage schedule of gold compounds which we now employ is as follows: We use Solganol-B Oleosum, which is aurothioglucose. We start with small doses, 10 mg., and then increase to 25 mg. and, if tolerated, to 50 mg. at weekly intervals, and continue at 50 mg. weekly until the patient has received 1.0 Gm. of the compound. If the patient has shown improvement and has had no untoward toxic effect, the gold is continued, 50 mg. every two or three weeks. At the onset of any toxic manifestation, the gold is discontinued. Depending on the severity of the toxic reaction, gold may not be given again or it may be resumed in smaller amounts. We have not had the courage to resume gold following severe toxic reactions, such as a rash, so we cannot say that once a patient has had a severe reaction that patient is permanently sensitized to gold. It would appear that a patient who has had the disease for more

than two years is more likely to develop, a toxic reaction than an early case. The toxic reactions can persist for long periods. Several of the dermatitides have lasted for over two years. We have had two deaths (in over 400 gold-treated cases) which could be attributed directly to gold, one due to aplastic anemia and the other to thrombocytopenic purpura.

Patients with rheumatoid arthritis and psoriasis respond less favorably to gold than those who do not have associated psoriasis. Rheumatoid arthritis of the spine, or ankylosing spondylitis of the Marie-Strumpell type, does not respond at all to chrysotherapy.

DR. PUTNAM C. LLOYD: Is there anything known of the mechanism of the action of gold in rheumatoid arthritis?

DR. RAGAN: The original work done by Feldt was begun because of the clinical similarity between rheumatoid arthritis and tuberculosis. In 1914, gold was found to be bacteriostatic and recently Dawson and Hobby showed that gold was bacteriostatic against group A hemolytic streptococci. Until the pathogenesis of the disease is more clearly understood, I am afraid we will know no more of the mechanism of the action of gold. We have suggestive evidence that relapse may be associated with the elimination of gold. We do know that gold must be combined with a sulfhydryl group to be effective. This may have a bearing on its mechanism or it may be due solely to the fact that gold compounds, to be soluble at a pH around 7, must be in the gold-thiol form.

STUDENT: Is there any way to avoid toxic reactions?

DR. RAGAN: We believe that we can decrease the incidence of stomatitis by not exceeding a weekly dose of 50 mg. of the compound. Hemopoietic toxicity such as thrombocytopenia and agranulocytosis can be kept at a minimum by frequent blood counts with estimation of the platelets on

the smear. Renal damage can be kept to a minimum amount by frequent urinalyses. The skin lesions are difficult to predict, some are preceded by an eosinophilia, some are not. All are preceded by a pruritus and at the first mention of pruritus, gold should be stopped. If the patient fails to develop a rash, we believe that by vigilance we may have avoided a severe dermatitis. However, most of the patients who develop pruritus go on to develop a rash of more or less severity even if the gold is stopped. We have a routine to which we adhere rather strictly. A patient receiving chrysotherapy has a white blood count with an estimation of platelets on the smear and a urinalysis every two to three weeks. I would again like to mention BAL, which promises to be fully as effective in combating gold toxicity as it is in arsenic and mercury poisoning.

DOCTOR: Do you believe that with adequate care, gold can be administered by the local medical doctor?

DR. BOOTS: We are somewhat reluctant to advocate the use of gold in general practice by physicians who have had no previous experience with it. Where we have sent patients from out of town back to their doctors with instructions on the administration of gold, we have found that more trouble developed than with patients we have followed ourselves. There are many alarms and excursions in the course of gold therapy and to evaluate these, it is important that the physician have considerable understanding of the eventualities which may develop. If a watch is kept over the blood count and urine and if gold is stopped at the first symptom of pruritus, sore mouth, or abdominal cramps, the physician who has not seen a lot of gold therapy should be able to carry out this form of treatment.

DR. RAGAN: The flexion contractures which develop in rheumatoid arthritis are a striking characteristic of the disease and the basis of many of the deformities. These, with the muscle atrophy and the micro-

scopic lesions in the muscle described by Freund, have led us to focus our attention on the skeletal musculature.

We have been fortunate in interesting Dr. Schlesinger of the Neurological Institute in this problem, and have asked him to discuss it for us today.

DR. E. B. SCHLESINGER: I have been asked to discuss the problem of muscle spasm in rheumatoid arthritis. There are few terms in clinical medicine which are so misused or which can evoke so much controversy as muscle spasm. We ought, therefore, first define our terms. Loosely, muscle spasm is a reflex defense phenomenon, a prolonged contraction not amenable to voluntary control, characterized by resistance to stretch and by diffuse, severe, poorly localized pain. How does this state come about? There are many possible mechanisms which may act as the initial stimulus. First, we may have actual irritation of the sensory nerve endings in the muscle mass itself. This may be due to mechanical trauma or inflammatory exudate. Secondly, muscle spasm may represent protective splinting of a neighboring joint which is the seat of disease. Lastly, the abnormal state of contraction may be secondary to changes in other parts of the neural arc, such as in the posterior columns, posterior root or sensory ganglion. Pathologic changes in these structures may lead to hyperesthesia, pain and diffuse tenderness in the muscle, which reacts by an attempt at shortening and immobilization.

All this may be worthy of further clarification. Normally, muscle stretch elicits afferent impulses arising in the muscle spindles. These impulses are conducted back to the cord, and a reflex contraction is then initiated by way of the motor side of the arc. This is the basic stretch reflex of Sherrington. When there is pathologic change somewhere in the system, there may be a potentiation of this cycle. The threshold of the arc is lowered, and the response becomes much more active than under normal

circumstances. Thus we have the mechanism for a self-perpetuating circuit, the vicious cycle of pain and splinting or spasm. Attempted stretch elicits pain and further splinting, then more pain, and so on. Now that we have roughly defined the probable mechanism, we may turn to the problem at hand.

In acute rheumatoid arthritis, one is struck by the severity of the muscle changes. Here, in addition to joint inflammation (which causes reflex splinting) there may be infiltration of the actual muscle mass by inflammatory exudate. Also, there may be changes in the peripheral nervous structures themselves. Thus we find many of the elements which lead to muscle splinting or spasm and its accompanying pain and deformity. The acute arthritic limb adopts a flexion position which represents an attempt to avoid muscle stretching and joint irritation. These positions, a defense mechanism, may be easily reversible early, but if allowed to persist, may become a major cause of deformity. We know that long fixation leads to atrophy of disuse.

We must emphasize that in attempting to influence these phenomena, we are not attacking the primary disease entity but merely its secondary manifestations. Nevertheless, such changes may leave the patient crippled permanently, even though his primary disease be in complete remission.

How do we propose to handle such a situation? We know that any agent which acts by relieving pain or avoiding movement is useful in symptomatic relief. Any form of therapy which invades or breaks up the vicious cycle of pain and spasm may dramatically alter the clinical picture. Promotion of absolute rest has many dangers and needs no discussion here. Heat, analgesics, local anesthetic blocks, etc., are time-tried and respected forms of treatment. Unfortunately, none are specific or reliable.

In an attempt to attack the problem more basically, we have turned to drugs which

have a specific relaxant effect on muscle. Curare is such a drug. The initial difficulties in obtaining a suitable preparation being solved by the development of a long-acting suspension of curare in oil and wax, it is quite logical to try curariform drugs in an attempt to reduce reflex shortening with its concomitant pain. We have been using such a preparation in various syndromes which have in common the entity of muscle spasm. Our results are in the right direction but unquestionably open to criticism if any final conclusions were to be drawn so early in the work.

DOCTOR: What beneficial effects have you obtained with curare suspensions in oil and wax?

DR. SCHLESINGER: Our patients seem more comfortable. They show greater mobility. They do not adopt marked flexor protective positions. They may not require as much analgesia or sedation. They seem to respond better to physical therapy. These are all clinical impressions and therefore of little objective value. There are, however, objective data, too, which indicate a beneficial effect of curare. Perhaps the most important are electrical studies. Briefly, a muscle at rest shows no electrical activity when studied by standard electromyographic technics. A normal muscle can be put at rest in full extension. Certain of our patients with rheumatoid arthritis, on the other hand, show consistent evidence of electrical activity, incident to reflex shortening, except in positions of pronounced protective flexion. We believe we can claim a therapeutic response when such patients gain full extension and in that position show no bursts of impulses representing attempted shortening. Such results are obtained with curare. The patient you have seen today (Mrs. S.) is a good example of the desired end result.

Another objective criterion is obtained by a study of urinary creatine output. During his visit here, Dr. Mortensen of Denmark

described to me his findings in a series of acute low back cases with severe muscle spasm. He was able to demonstrate a sharp rise in creatine output during the acute clinical phase and an abrupt fall in output when the clinical signs subsided. Adapting his technic to our problem, we have tried to study the changes which might occur in our patients with rheumatoid arthritis. There seems to be a rough correlation to date which may prove useful but much more work must be done.

DR. RAGAN: Gold is still a very controversial subject and curare is still new and experimental. However, there are certain broad concepts of treatment upon which I think almost everyone working in this field will agree and these should be stressed. Dr. Boots said he would talk about this part of the program.

DR. BOOTS: To state that we use chrysotherapy for rheumatoid arthritis often gives a wrong impression. It suggests that other forms of treatment have been discarded. Such is far from the truth.

Patients with early active disease are most suitable for gold therapy and best results are obtained in this group. Gold is discontinued immediately if any evidence of toxicity occurs. We do not like to administer gold to the elderly, to those with a history of liver or renal damage, or blood-dyscrasia. Excellent results are not as frequent when the disease is advanced and marked deformities have occurred. Also, we hesitate to use gold for patients whose family physicians have advised strongly against taking it. We do not use gold if the disease is quiescent. For the reasons outlined, probably not more than 60 per cent of the patients with rheumatoid arthritis in our clinic are started on gold therapy and of this number 10 per cent receive inadequate gold treatment because of early development of toxicity. In addition to gold this group is treated with the more conservative measures which are used for the non-gold treated patient.

What are these other methods of therapy? They consist chiefly of (1) measures which improve the general health of the patient, reduce fatigue, giving him a chance for spontaneous remission, (2) measures which give symptomatic relief, and (3) the prevention and correction of deformities.

The time allowed will not permit of detailed discussion of all of these, and we will limit ourselves to little more than their enumeration.

MEASURES WHICH IMPROVE THE GENERAL HEALTH OF THE PATIENT

A. Rest (or avoidance of fatigue) is almost as necessary for rheumatoid arthritis as for tuberculosis. The amount varies from complete bed rest for the severely ill patient who has a persistent fever, to an hour's rest period before dinner, or the simple avoidance of severe fatigue for the mildly ill.

B. Nutrition. The patient is usually thin and undernourished, sometimes to the point of emaciation, and a highly nutritious diet is essential. We frequently supplement such a diet with 2 tablespoonfuls of cod liver oil at bedtime. While it would seem sensible to give an abundance of vitamins, massive doses of any particular vitamin seems to be of no specific value. In recent years, vitamin D in capsules of 50,000 units have been widely and, in our opinion, unjustifiably recommended in advertisements. In our experience such preparations have been of no proven value in rheumatoid arthritis and sometimes result in severe and irreversible vitamin D poisoning.

C. Treatment of Anemia. Hypochromic anemia is frequently present and responds poorly to iron administration. Several transfusions of 500 cc. of blood to such patients will usually cause marked improvement.

D. Removal of Intercurrent Infections. Formerly there was thought to be a direct relationship between rheumatoid arthritis and foci of infection. We have been unable to prove any such relationship. However, the

eradication of infections, such as periapical abscesses and chronic sinus infections, helps the general health of the patient.

E. Climate. The prevalent opinion is that the disease rarely occurs in tropical climates. No well controlled experiment has ever been done of sending patients to the tropics but it would seem that this offers definite possibilities provided the patient can live as comfortably in such regions as in his home.

F. Psychotherapy. An optimistic attitude on the part of the physician is very helpful. These patients are easily depressed and it seems as though there is some relationship between their mental depression and increase in their symptoms.

MEASURES WHICH GIVE SYMPTOMATIC RELIEF

A. Analgesics and Sedatives. There is no proof that salicylates have any direct effect upon the course of rheumatoid arthritis but they offer considerable relief of the pain. Salicylates are of real value in giving the patient increased rest and comfort, and, as far as we can tell, do no harm.

B. Physiotherapy. Physiotherapy is of much more value for osteoarthritis than rheumatoid arthritis but it probably has no real effect upon the course of the latter disease. However, such measures as compresses or flaxseed poultices to a painful joint often offer relief.

PREVENTION AND CORRECTION OF DEFORMITIES

Much can be done by the internist in the prevention of contracture deformities by the use of posterior splints, applied for varying periods each day. These deformities are in large part due to muscle spasm and it may be that the use of curare in conjunction with exercises within pain limits as described by Dr. Schlesinger, will prove of equal value. The correction of deformities which have already occurred lies mostly in the

field of the orthopedic surgeon and will not be discussed at this time.

DOCTOR: I am not clear as to your opinions on the value of rest in the patient with rheumatoid arthritis.

DR. RAÇAN: At the present time we believe that we cannot be too dogmatic upon this point. Rest has been one of the most trusted standbys in the treatment of rheumatoid arthritis and its value in diminishing pain, fever and evidence of activity of the disease process is unequivocal.

However, we believe that rest should be supervised. To tell a patient to go home to bed or to hospitalize a patient and prescribe strict bed rest can be very detrimental. The group at Cornell have shown that, in normal males with bed rest in a plaster spica, definite changes in the metabolism of the patient occur. Notably, a negative nitrogen balance sets in. Clinically, we know that muscle atrophy and osteoporosis are associated with continued inactivity. A patient with active rheumatoid arthritis confined to bed lies in a position of inactivity almost comparable to a body spica because of voluntary splinting of the painful joints. We believe that exercises within the limits of pain and fatigue can be carried out in such patients. In conjunction with adequate salicylate therapy to control pain and curarization to combat the element of muscle spasm the range of motion can be extended. This effort to decrease the muscle atrophy in rheumatoid arthritis is still in progress and a conclusive evaluation of the results cannot be made at this time but the preliminary results are encouraging.

SUMMARY

Rheumatoid arthritis is a common disease of unknown etiology, subject to remissions and exacerbations, characterized clinically by striking involvement of the joints and, to a varying degree of other systems, and demonstrated pathologically to be a disorder of connective tissue. Presenting certain

common features with rheumatoid arthritis are serum sickness, rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa and scleroderma. Despite clinical and pathological similarities, it is not implied that all these disorders have a common etiology.

The clinical picture of rheumatoid arthritis is well known. Cases are presented which serve to emphasize the multiplicity of systems involved as well as the overlapping of the other mesenchymal diseases in the clinical picture of rheumatoid arthritis.

Because the connective tissue appears to be the common denominator throughout this discussion, the nature of its two main subdivisions was considered. The three types of fibrous elements, collagenous, reticulin and elastic fibers are known to be denatured, insoluble proteins of high molecular weight. The cement substances on the other hand are made up of compounds or complexes of proteins with highly polymerized mucopolysaccharides. Hyaluronic acid, hyaluronosulfuric acid, chondroitin sulfuric acid and the amyloid sulfuric acid ester are the only four polysaccharides yet identified. All are of high molecular weight and their exact composition is unknown. Specific enzymes called hyaluronidases exist in the mammalian body, as well as in many other natural sources, which possess the specific power of depolymerizing and hydrolizing hyaluronic acid and perhaps other polysaccharides. While all these substances are presumably concerned with the diseases under discussion, their normal physiology and pathological variations have not yet been worked out.

In some patients with rheumatoid arthritis, hyaluronate is increased in the synovial fluid but what significance this observation has remains to be determined.

When considered pathologically, rheumatoid arthritis presents two chief charac-

teristics. One is the granulomatous lesion of connective tissue with necrosis, round cell infiltration, palisading and giant cell reaction contributing to nodule formation. This may be grossly seen subcutaneously about the elbows or may be only microscopically visible in the connective tissues of nerves, blood vessels and muscle. The other lesion is essentially the same but because it involves the connective tissues of joints—the synovial, capsular and subchondral tissues—results first in an acute inflammation and later in destruction of the joint. The clinical findings of redness, heat, swelling, pain, joint deformity, muscular spasm and atrophy, and subcutaneous nodules thus all have a common pathological basis. When this process is widespread the general manifestations of fever, weakness, anemia, weight loss, cardiac, renal, lymphatic and eye disease may also be understood.

Klinge has postulated that the initial lesion of rheumatoid arthritis involves the connective tissue cement substance. At the present time no etiological agent or mechanism is known. The hemolytic streptococcus theory has as yet resulted only in the diagnostic group A streptococcus agglutination reaction which is positive in about 55 per cent of cases of rheumatoid arthritis but which may be a non-specific reaction. As yet no virus etiology can be regarded as established nor has the possibility of allergy, bacterial or otherwise, though attractive, ever been placed on tenable grounds. Much of the difficulty lies in the fact that the disease as yet cannot be experimentally produced either in man or animal.

The problem of therapy is unsolved. The status of gold therapy is difficult to evaluate. Five to 10 per cent of patients develop early toxic reactions which preclude therapy. It may be possible to avoid stomatitis and renal damage by moderate dosage but the toxic reactions of the skin are unpredictable and not yet controllable. Ten

to 20 per cent of patients receive no benefit from therapy. Forty to 60 per cent are definitely improved but of these 80 to 90 per cent relapse in a five-year period. Continuous treatment with gold to avoid these recurrences is now being tried.

It is believed that in the early cases of true rheumatoid arthritis, gold is the best means of therapy. In the Edward Daniels Faulkner Arthritis Clinic at the Presbyterian Hospital, about 50 per cent of patients with rheumatoid arthritis do not receive gold therapy either because of contraindications to gold therapy or because it is refused by the patient. About one-half of these show some improvement, whether due to the general measures instituted or to a spontaneous remission. Supportive measures include those directed at improving the general health of the patient: adequate rest, high vitamin and caloric diets, transfusions and the treatment or removal of intercurrent disease. They include psychotherapy to attempt to ease mental burdens and adjust the patient to his disease. Heat, salicylates and sedatives may make the acute stages less difficult while physiotherapy and appliances to prevent and correct deformities tend to improve the latter situations. Finally, because of the rarity of the disease in the tropics, the removal of the patient to the tropics should be considered where the status of the patient permits.

One interesting approach, novel but promising, is the use of curariform drugs. Based on the premise of a self-perpetuating vicious cycle of pain and muscle spasm initiated by reflex stimuli from diseased joints, muscle or the nervous reflex arc, a long-acting preparation of curare in oil and wax is employed to induce relaxation of muscle. Clinical improvement seems to follow and objective studies by electromyographic technics and creatine excretion, which are still being evaluated, tend to be corroborative.

Clinico-pathological Conference

Chronic Granuloma*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. C., was a sixty-five-year old white male hotel executive, who entered the Barnes Hospital for the first time on February 12, 1946, complaining of generalized itching, cough and loss of weight. The family history was non-contributory. The patient stated that he had always been well until the onset of the present illness. Two years before entry he underwent bilateral inguinal herniorrhaphy without event. About eight months before admission he noted the onset of lacrimation which at times was intense; it was more pronounced on the left.

Six months prior to entry the patient developed a pruritic eruption on his legs. One month before admission the lesions became red and raised. The pruritus became generalized and so severe that the patient could not rest day or night. He was seen by a dermatologist who made a diagnosis of scabies but the lesions did not respond to specific treatment. Subsequently they resembled erythema multiforme and finally they took on the characteristic appearance of erythema nodosum. During the month before entry the patient noted increasing weakness and he felt feverish. His physician noted that he had temperature elevations as high as 101.6°F. on several occasions. During the six months before admission the patient lost 17 pounds. Two weeks before admission he had a sore throat

which persisted for several days. Concomitantly the patient developed a cough which was productive of thick mucoid sputum. He had several profuse sweats and an occasional slight chill.

On physical examination at the time of entry, the patient's temperature was 37°C., pulse 90, respirations 18, and blood pressure 140/70. He was an elderly man who appeared pale and chronically ill. There were numerous excoriations on the skin. Over the lower extremities, and to a lesser degree over the upper ones, red, raised, tender nodules, 2 to 3 cm. in diameter, surrounded by a zone of erythema, were present. A few lymph nodes were palpable in the left posterior cervical chain and large, firm, freely movable nodes were felt in both axillary and inguinal regions and in the left epitrochlear region. There was chemosis of the right eye and the conjunctiva was inflamed. The left eye was similarly involved but to a lesser degree. The pupils reacted normally to light and accommodation. The right fundus appeared normal; the left could not be visualized. The left auditory canal was filled with green, foul-smelling débris. The drum was thick and no landmarks were visible. No perforation was seen. The nasal mucosa was reddened. The throat appeared normal. The epiglottis was red and thickened; the left vocal cord was fixed in the cadaveric position. The

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lungs were clear to percussion and auscultation. The heart was not enlarged; the rhythm was regular. A harsh, grade II systolic murmur was heard at the apex and at the aortic area. The liver was felt 2 cm. below the right costal margin; neither the spleen nor the kidneys were palpable. The physical examination was otherwise within normal limits.

Laboratory data were as follows: Blood count: red cells, 3,400,000; hemoglobin, 10.4 Gm.; white cells, 7,100; differential count: eosinophiles, 11 per cent; stab forms, 1 per cent; segmented forms, 67 per cent; lymphocytes, 21 per cent. Urinalysis: negative except for an occasional red blood cell per high power field. Stool examination: negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; total proteins, 7.7 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 4.4 Gm. per cent. Blood culture: no growth. Heterophile agglutination test: negative. Sputum examination: no tubercle bacilli seen. Bone marrow: stimulation of myeloid cells with a shift to the left; 7 per cent plasma cells and 2 per cent reticulum cells were present. Cephalin-cholesterol flocculation test: 1+. Roentgenogram of the chest: "The cardiac silhouette is within normal limits as is the aorta. There is a plaque of calcium in the aorta. Hilus shadows are quite prominent suggesting large lymph nodes. Lung markings are somewhat coarse and feathered; they extend out from the hilus on both sides. The parenchyma is clear." Gastrointestinal series: indeterminate. Cholecystogram: normal gallbladder. Electrocardiogram: slight notching was present and there was a Q wave in Leads I and IV; interpretation: myocardial damage.

During his hospital stay the patient's temperature rose daily, usually reaching 39°C. and occasionally 40°C. The pulse rate rose and fell consistently with the

temperature curve; the respiratory rate was normal. Soon after admission, a lymph node was removed from the right axilla. The microscopic sections showed considerable hyperplasia of the lymphoid elements but the general architecture remained unchanged. A moderate number of eosinophiles was seen and there was some increase in fibrosis but no Dorothy Reed cells were visible. The epithelium was normal. A diagnosis of "reticular hyperplasia" was made.

The patient received repeated transfusions and was given a short course of roentgen therapy to the lymph nodes which gradually became smaller. The skin lesions varied in intensity but were never completely absent. Pruritus was a constant, distressing symptom. Shortly after admission, the patient's cough increased, and showers of crepitant inspiratory râles were heard at the base of the right lung. Penicillin therapy was given but the cough continued unabated. Many specimens of sputum were examined for tubercle bacilli but none were found. Numerous blood counts were not significantly different from those on admission except that the eosinophiles were reduced. Repeated cultures of the blood were sterile. A chest film taken about two months after entry showed considerable increase in the prominence of the hilar shadows on the right. The pulmonary markings were also accentuated in the right lung more than previously, and there was infiltration about the bronchial and vascular markings. Impression: "bronchopneumonia, right lung." The patient failed to improve, and on discharge he retained most of the symptoms present at the time of admission. He left the hospital on April 20, 1946.

He continued to do poorly at home; his fever persisted and the skin lesions did not improve. While at home he was given two injections of anti-reticular cytotoxic serum.

He reentered the Barnes Hospital on May 4, 1946.

At the time of entry, the patient's temperature was 38.3°C., pulse 90, respirations 24, and blood pressure 130/64. He appeared extremely ill; he was weak and emaciated. The skin was hot, generally atrophic and slightly icteric. Areas of brown pigmentation were noted over the trunk at the site of previous lesions. On the forearms there were several small movable nodules with slight surrounding erythema. One was present on the dorsum of the left hand. There were also pustules scattered over the skin. The auricle of the left ear was somewhat swollen, red and tender to the touch. Moderate contracture deformities at the elbows and knees were present. There was no significant lymphadenopathy. The eyelids were slightly swollen; the palpebral conjunctivae were pale and small pin-point yellow papules were present on their surface. Examination of the lungs revealed dullness to percussion, bronchial breath sounds and medium râles at the right base posteriorly. There was a soft, grade II systolic murmur at the apex. The liver edge was felt 4 cm. below the right costal margin. The spleen was not palpable. Neurological examination showed flattening of the right side of the face. The tendon reflexes were all hyperactive.

Laboratory studies were as follows: Blood count: red cells, 3,360,000; hemoglobin, 10.7 Gm.; white cells, 6,850; differential count: eosinophiles, 1 per cent; stab forms, 13 per cent; segmented forms, 55 per cent; lymphocytes, 28 per cent; monocytes, 3 per cent. Urinalysis: albumin, trace; sediment, occasional white blood cell per high power field. Stool examination: negative. Coccioidin skin test: negative. Culture of skin pustules: non-hemolytic staphylococcus; cultures for fungi were negative.

The patient received anti-reticular cytotoxic serum and transfusions. His tempera-

ture ranged between 38°C. and 40°C. The skin manifestations noted on entry persisted; in addition, lesions characteristic of erythema nodosum recurred. A decubitus ulcer developed over the coccyx. A fluctuant, subcutaneous mass was noted in the left axilla from which thick pus was aspirated. The patient was discharged unimproved on June 1, 1946.

Because of the investigations on the treatment of lymphomas with nitrogen mustard compounds at another university clinic, the patient was transferred to that institution. There the physical findings were identical with those recorded on the patient's last Barnes Hospital admission.

Studies were as follows: Blood counts: unchanged from those noted previously. Total proteins, 7.1 Gm. per cent; albumin, 2.1 Gm. per cent; globulin, 5.0 Gm. per cent. Cultures of skin lesions for fungi: negative. Roentgenogram of the chest: "Enlargement of both hilar shadows, extensive pulmonary infiltration in both lungs, more on the right."

The skin lesions were biopsied and the sections were studied by several pathologists. No definite diagnosis was made but an "atypical lymphoma" seemed most likely. Because the diagnosis could not be definitely established, therapy with a nitrogen mustard derivative did not seem justified. The patient was given iodides with some improvement in the appearance of the skin lesions. He was discharged and returned immediately to the Barnes Hospital where he was admitted for the last time on July 5, 1946.

At the time of entry the patient's temperature was 39.2°C., pulse 130, respirations 40. He was emaciated, pale, and appeared *in extremis*. There was slight icterus of the sclerae. The skin was atrophic and large areas of brown pigmentation were noted. Numerous ulcerations including the decubitus over the coccyx were present. The

tongue was red and dry. Signs of fluid were noted at the right lung base. Otherwise the physical findings were unchanged from those of the previous admission.

Laboratory data included the following: Blood count: red cells, 2,830,000; white cells, 2,750; differential count: eosinophiles, 2 per cent; stab forms, 38 per cent; segmented forms, 37 per cent; lymphocytes, 19 per cent; monocytes, 4 per cent.

The patient failed rapidly and died on July 6, 1946, twenty-four hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presented such a difficult problem that despite very thorough study a definite diagnosis could not be made during the patient's long illness. Four aspects of the illness were most prominent; first, the distressing pruritus and several skin lesions; second, the persistent fever; third, the lymphadenopathy; and finally, the hyperglobulinemia. Dr. Weiss, would you comment on the skin lesions and their relation to the underlying disease?

DR. RICHARD S. WEISS: I first saw this man in January, 1946. He complained of extreme pruritus but the skin lesions at that time were not striking. The only finding was the presence of excoriations which in some respects resembled those seen in scabies. The distribution of the lesions, however, was not typical of scabies. Nevertheless, I prescribed anti-scabetic treatment; the patient returned in one week and stated that he was very much better. He then developed urticaria and lesions characteristic of erythema multiforme. Subsequently erythema nodosum was noted. Several weeks later when I again saw him, he looked quite ill and complained bitterly of pruritus. His temperature was slightly elevated and there was alarming lymphadenopathy which led me to the conclusion

that the patient had a serious systemic disease, possibly Hodgkin's disease or one of the lymphomas. I therefore recommended that he be hospitalized for more detailed study.

DR. HAROLD SCHEFF: It is of interest that a differential blood count done at that time showed a 10 per cent eosinophilia.

DR. ALEXANDER: Do you attribute the eosinophilia to the skin manifestations, Dr. Weiss?

DR. WEISS: Eosinophilia occurs in many generalized skin diseases. In cases of lymphoma with involvement of the skin the eosinophilia is usually more profound than was recorded in this instance.

DR. ALEXANDER: It may be concluded, I presume from your observations, Dr. Weiss, that the patient definitely exhibited the lesions of erythema multiforme and erythema nodosum. Attention has been called to the fact that the patient had generalized lymphadenopathy and one of the nodes in the right axilla was removed for study. Dr. Moore, would you describe the microscopic sections cut from the surgical specimen.

DR. ROBERT A. MOORE: The first lantern slide (Fig. 1) shows a section of the skin removed. The thickness of the epidermis was approximately normal. There was slight edema of the dermis about the blood vessels and about some of the accessory structures of the skin not shown in the section. A cellular infiltration, consisting largely of the cells of the mononuclear series, was noted. The diagnosis on the basis of these findings was chronic inflammation of the skin. The second slide (Fig. 2) is that of a section of the lymph node; it shows the capsule of the node with the associated vascular and lymphatic spaces. There was hyperplasia of the follicles of the node, but the cellular types present within the node were normal, and there was only slight cellular infiltration of the capsule. The pathologic diagnosis was hyperplasia and chronic in-



FIG. 1. (No. 46-1194). Microscopic section of skin removed at the time of lymph node biopsy. The changes are those of chronic inflammation. $\times 47$.

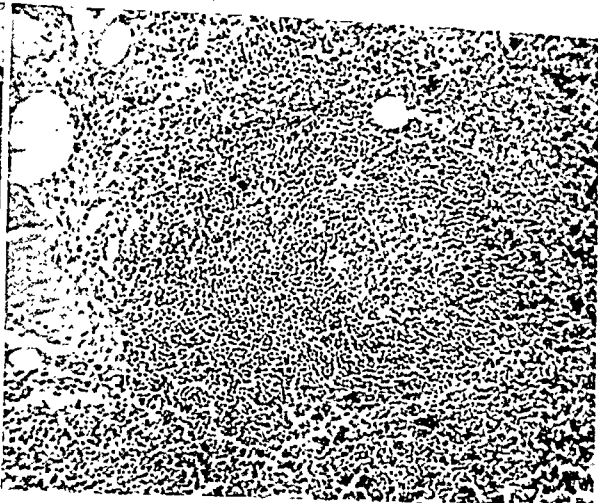


FIG. 2. (No. 46-1193). Microscopic section of lymph node showing follicular hyperplasia. $\times 47$.

flammation of the lymph node. In neither the skin nor the lymph node were there any changes characteristic of a specific disease entity.

DR. ALEXANDER: From the information available, Dr. Moore, do you believe that the diagnosis of lymphoma is likely?

DR. CARL V. MOORE: It is our opinion that either reticulum cell sarcoma or Hodgkin's disease was the most likely possibility. Against the former was the fact that the lymph node did not show characteristic changes; against the latter was the fact that the patient never had a lymphopenia. Although there is no definitive blood picture in Hodgkin's disease, frequently a lymphopenia is noted during some phases of the disease.

DR. ALEXANDER: Is it true that in Hodgkin's disease a leukocytosis may occur?

DR. C. V. MOORE: That is correct. The white cell count may range from a leukopenic level to counts of 150,000 or more.

DR. ALEXANDER: The bone marrow was reported as showing stimulation of the myeloid elements. Would you comment on the significance of this finding.

DR. C. V. MOORE: Myeloid stimulation such as was observed here is compatible with almost any inflammatory disease.

DR. ALEXANDER: If this patient had one of the lymphomas, for example lympho-

sarcoma, would the lymph nodes be expected to show characteristic histologic changes.

DR. EDWARD H. REINHARD: Yes, they would. However, I have seen instances in which the first lymph node biopsies from patients with lymphosarcoma or with Hodgkin's disease failed to show definitive lesions whereas subsequent biopsies showed the characteristic histological changes. In lymphosarcoma, however, there is usually tremendous proliferation of the lymphocytes with destruction of the architectural pattern and, very frequently, invasion of the capsule.

DR. ALEXANDER: Is it correct to say that frequently in Hodgkin's disease the characteristic lesions may not be seen in lymph nodes in certain phases of the disease whereas in lymphosarcoma, if there is lymphadenopathy, pathologic changes in the lymph nodes will be present in most cases.

DR. REINHARD: I think that is correct.

DR. ALEXANDER: Therefore, in this case, if a diagnosis of lymphosarcoma cannot be made from the microscopic sections of the lymph node removed from the patient's axilla, it may be inferred that in all probability the patient did not have lymphosarcoma. Dr. Moore, do you feel that the diagnosis of Hodgkin's disease is still tenable despite the lymph node findings?

DR. C. V. MOORE: Yes.

DR. ALEXANDER: The skin lesions were consistent with Hodgkin's disease. The fever was persistent for many many months. If there is high fever in Hodgkin's disease, is it necessarily of the Pel-Ebstein type or may it be continuous?

DR. C. V. MOORE: The fever is not continuous as a rule, but it may be.

DR. ALEXANDER: Would you agree that the blood picture and bone marrow findings do not suggest leukemia?

DR. C. V. MOORE: They most certainly do not.

DR. ALEXANDER: Dr. Scheff, you and Dr. Womack saw giant cells in the microscopic sections of the lymph node. Did you think that the findings in the section were compatible with a diagnosis of tuberculosis of the lymph nodes?

DR. SCHEFF: We did not think so.

DR. ALEXANDER: Dr. Goldman, would you comment on generalized lymphadenopathy in tuberculosis. Is there an adenopathic type of generalized tuberculosis, and if so, is it common?

DR. ALFRED GOLDMAN: Generalized lymphadenopathy does occur in generalized tuberculosis but it is not very common.

DR. ALEXANDER: Dr. Bottom, did the chest roentgenogram indicate to you that this patient had tuberculosis?

DR. DONALD S. BOTTOM: He has had tuberculosis, but I believe the present findings are indicative of a quiescent tuberculous lesion in the lungs.

DR. ALEXANDER: Does generalized adenopathy as a manifestation of tuberculosis occur in any particular age group?

DR. GOLDMAN: It may occur in patients at any age, but it usually occurs in patients in the younger age groups.

DR. ALEXANDER: It would be quite rare, then, in a patient as old as this one.

DR. GOLDMAN: Yes. That is one of the reasons why Hodgkin's disease seems more likely in this case. However, some of the findings are compatible with sarcoidosis

and that diagnosis should be considered. Generalized lymphadenopathy is common in sarcoidosis.

DR. ALEXANDER: The apparent enlargement of the hilar lymph nodes is also in keeping.

DR. GOLDMAN: I am not able to state whether the skin lesions seen in this patient are compatible with Boeck's sarcoid. Perhaps Dr. Weiss would discuss that point.

DR. WEISS: The skin lesions were not consistent with those seen in sarcoidosis. Usually the skin manifestations of sarcoid are moderately hard, flat plaques or nodules; they have no tendency to suppurate and they are usually situated adjacent to the joints.

DR. ALEXANDER: Are there other features in this case suggestive of sarcoidosis?

DR. W. BARRY WOOD, JR.: The eye findings certainly should be mentioned.

DR. ALEXANDER: That is a good point. We have no specific information about the uveal tract, but the eye signs were prominent in the clinical course.

DR. WOOD: In the cases of sarcoid described by Dr. Longcope, the initial symptoms were frequently related to the eye. That was true in this case. Further, it has been emphasized by many writers that the serum globulin tends to be extremely high in sarcoid, and I think that the hyperglobulinemia here is another point in favor of Dr. Goldman's suggestion. Against the diagnosis of sarcoid, however, is the relatively malignant course of this patient's illness. I would therefore postulate that if the patient had sarcoid, he probably had tuberculosis, too; the two diseases are not infrequently seen together at postmortem examination.

DR. ALEXANDER: Tuberculosis involving what organs?

DR. WOOD: I cannot specify where Dr. Moore will find the tubercle bacilli, Dr. Alexander, but I think active tuberculosis would explain the relatively rapid course of

the illness; sarcoid alone without tuberculosis usually runs a more benign course.

DR. ALEXANDER: Am I clear, then, that you believe the patient had both sarcoid and tuberculosis rather than tuberculosis alone.

DR. WOOD: Yes, I think that such a combination is likely in this case.

DR. ALEXANDER: Certainly sarcoid and tuberculosis occur together frequently; indeed some writers believe that they are the same disease.

DR. WOOD: Dr. Futcher followed some of the cases of sarcoid in Baltimore, and I would like to ask him whether or not pruritus was a prominent feature.

DR. PALMER H. FUTCHER: I do not recall that it was.

DR. ALEXANDER: When sarcoid is complicated or followed by tuberculosis, does the tuberculous process occur at the site of the sarcoid lesion, or do they occur apart from one another?

DR. ROBERT A. MOORE: I belong to the group which believes that sarcoid and tuberculosis are two independent diseases. My answer to the question, therefore, would be that although tuberculosis may occur in a patient with sarcoid, the sarcoid lesions do not become tuberculous.

DR. ALEXANDER: Dr. Reinhard, would you discuss the anti-reticular cytotoxic serum which this patient received.

DR. REINHARD: Anti-reticular cytotoxic serum is prepared by immunizing animals—horses or rabbits—with a mixture of human bone marrow and lymph node or spleen. The serum presumably contains antibodies against human reticulo-endothelial cells. Bogomolets, who developed the serum, claims that small amounts stimulate the reticulo-endothelial tissues of the body, whereas larger doses are destructive. He advocates the use of the serum as a means of avoiding the changes of senility, and also in treating diseases of the reticulo-

endothelial system; in the latter he advises larger doses in order to destroy those tissues.

DR. ALEXANDER: Would you comment on the clinical experience with the serum.

DR. REINHARD: There have been extremely few clinical results reported; most investigations to date are reported in the Russian literature. In this country there is confirmatory evidence, from experimental work, that the serum does have a potent antibody which will affect the growth of reticulo-endothelial cells in tissue culture.

DR. ALEXANDER: Is it generally available?

DR. REINHARD: No. We obtained it from a commercial laboratory which supplies it for investigational use only, and we were told very little about the method of preparation. We were told only how much of the serum to give, at what interval to give it, and that the treatment should not be repeated in less than six weeks.

DR. ALEXANDER: What about experience with the nitrogen mustard compounds in Hodgkin's disease and other lymphomas?

DR. REINHARD: The evidence published to date indicates that the nitrogen mustards have a definite beneficial effect in Hodgkin's disease and perhaps in other lymphomas. The remissions which are induced by nitrogen mustards do not last as long as those following x-ray, and the compounds are certainly at least as damaging to other normal structures as x-ray; I believe that most of the investigators who are studying the nitrogen mustards now feel that they may be useful in cases resistant to x-ray. However, one should emphasize that such patients rapidly become resistant to nitrogen mustard also.

In regard to the diagnosis, Dr. Alexander, either a fungus infection or tuberculosis seem very strong possibilities to me.

DR. ALEXANDER: The possibility that this patient was afflicted with a fungus infection was entertained very seriously. Cultures were made on Sabouraud's media

but were unrevealing. Likewise coccidioidin skin tests were done. In regard to tuberculosis I should like to ask if erythema multiforme occurs commonly in tuberculosis.

DR. WEISS: Not commonly, but it is seen occasionally.

DR. ALEXANDER: It has been taught that when one sees erythema nodosum, one must think of rheumatic fever or tuberculosis. Actually, erythema nodosum may be seen with a variety of infections.

DR. ROBERT ELLIOTT: It has been pointed out that uveo-parotid fever may be one of the manifestations of Boeck's sarcoid; however, I believe that erythema nodosum is not common in sarcoidosis.

DR. PAUL O. HAGEMAN: It seems to me that there are two points supporting the diagnosis of neoplasm in this case; one, the paralyzed vocal cords; and two, lymph nodes which receded with x-ray therapy. These two points lead me to favor the diagnosis of Hodgkin's disease.

DR. CARL V. MOORE: Dr. Alexander, a thorough search was made for acid-fast organisms in this man's sputum and none was found. Likewise the bone marrow preparations were examined for acid-fast organisms with negative results. I would like to ask whether the lymph nodes were stained for acid-fast organisms.

DR. SCHEFF: No, they were not.

DR. ALEXANDER: In summary, it may be said that there appears to be little unanimity of opinion among the staff as to the diagnosis. Hodgkin's disease was considered the most likely diagnosis when the patient was in the hospital and is still favored by some. Others have expressed the opinion that the patient was suffering from tuberculosis or Boeck's sarcoid or possibly from both. We have apparently been unable to assemble conclusive evidence in favor of any one of these possibilities. We are forced, therefore, to ask the pathologists to enlighten us as to the correct diagnosis.

PATHOLOGIC DISCUSSION

DR. ROBERT A. MOORE: From the gross findings the diagnosis at the time of the autopsy was a granulomatous disease involving particularly the right lung, and to a lesser extent, the liver, the spleen and the porta-hepatic lymph nodes. The real problem, therefore, was to identify the nature of this granulomatous process. Examination of the microscopic sections was necessary to determine the diagnosis. Figure 3 shows a section of one of the nodules in the lung. The lesion is distinctly granulomatous; there is necrosis in the center and in some areas there is caseation. Surrounding some of the nodules fibrosis is seen and there is an occasional giant cell about the edge of the nodule. There are epithelioid cells with finely vacuolated cytoplasm in the periphery. Essentially normal pulmonary tissue lies adjacent to the nodule.

In Figure 4 another nodule is seen with greater magnification. There is necrosis in the center of a group of epithelioid cells; at the periphery, fibrosis is developing. There are numerous capillary vessels in the young proliferating fibrous tissue. An acid fast stain showed acid-fast bacilli at the center of the necrotic foci in the lungs and other organs.

Figure 5 is a section of the surrounding lung showing a mononuclear exudate in the alveoli and proliferation within the alveolar wall. In other words there was a tuberculous pneumonia about the granulomatous lesion in the right lung.

In Figure 6 a section of a tracheobronchial lymph node is seen; there is complete caseation of the central part of the lymph node with slight cellular infiltration in the capsule. This type of lesion in a tracheal-bronchial lymph node is seen in first-infection tuberculosis. In other words, there is massive caseation of the lymph node extending to the capsule with a sharp line of

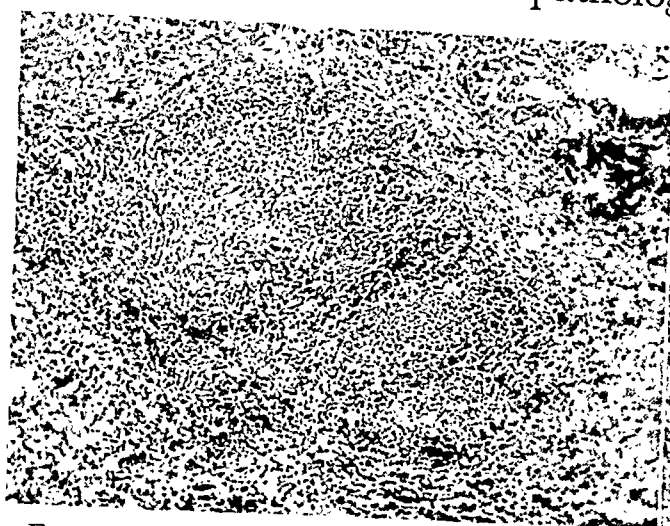


FIG. 3. (No. 46-1204). Microscopic section of a pulmonary nodule showing necrosis and caseation with peripheral fibrosis. $\times 47$.

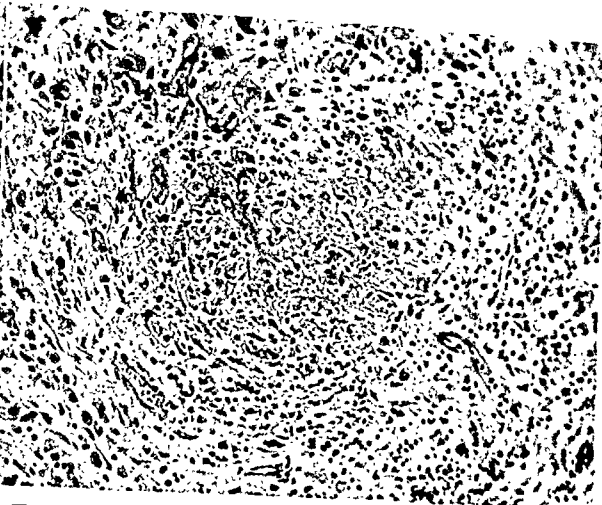


FIG. 4. (No. 46-1197). Microscopic section of a pulmonary nodule under higher magnification. Note the central necrosis and peripheral fibroblastic and capillary proliferation. $\times 97$.

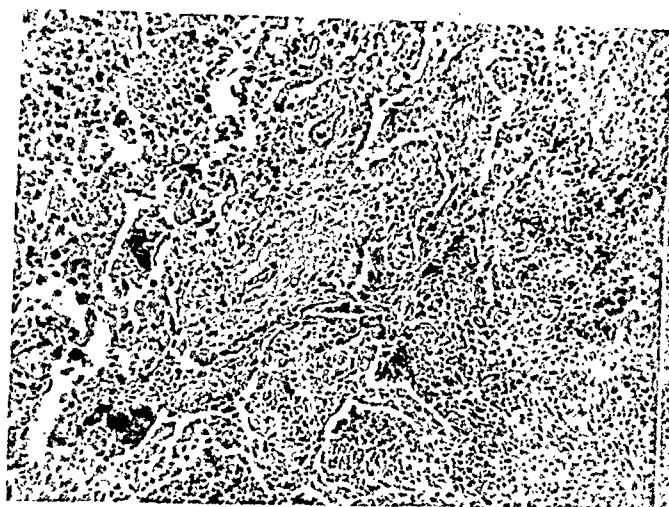


FIG. 5. (No. 46-1198). Microscopic section of an area in the right lung showing a mononuclear exudate. $\times 47$.



FIG. 6. (No. 46-1196). Microscopic section of a tracheobronchial lymph node. Note central caseation and the sharply demarcated fibrous tissue capsule. $\times 47$.

demarcation between the fibrous tissue of the capsule and the caseous lymphoid tissue.

Figure 7 pictures a section of the spleen showing a similar necrotic granulomatous lesion in the splenic pulp. Here, in contrast with the pulmonary lesions, there is practically no reaction about the focus of necrosis, no epithelioid cells and no fibrosis, but the necrotic area extends directly to join the splenic pulp. There were acid fast-bacilli in the necrotic nodules. Thus, in the lung, in the spleen and in the liver there was necrosis of tissue and the lesion was of the type described as necrotizing tuberculosis. The tubercles were necrotic rather than caseous. Under higher magnification the

character of the necrosis could be seen; numerous strands of fibrin permeated the necrotic areas. In caseous tuberculosis threads of fibrin are not seen.

Sections of the pericardium indicated that it was involved by the tuberculous process; so-called lymphocytic tubercles were identified in the pericardium.

In Figure 8, another variant of the reactions of tuberculosis is seen; the section is taken from one of the ulcers in the skin of the thorax. A blood vessel is shown; it is thickened in parts because of edema and because of cellular infiltration. Such a lesion with the marked intimal proliferation is representative of tuberculous granulation



FIG. 7. (No. 46-1199). Microscopic section of nodule in spleen showing necrosis and absence of cellular reaction about the focus. $\times 47$.

FIG. 8. (No. 46-1202). Microscopic section from a skin lesion showing characteristic reaction of a blood vessel in tuberculosis.

tissue. Characteristically, it is seen in the meninges and may at times be the only histologic evidence on which the diagnosis of tuberculosis is based. The lesion is not frequently seen in other viscera.

The bone marrow showed hyperplasia, particularly of the red cell series, but there were no granulomatous lesions in the marrow; it is understandable, therefore, that no acid-fast bacilli were found in smears of the marrow. In the testis there was hemorrhage into the interstitial tissue and atrophy of the seminiferous tubules; the latter change occurs in patients suffering from chronic debilitating disease. The spermatogonia and the cells of the spermatogenic series were entirely absent; the centers of the seminiferous tubules were filled with cells of the Sertoli type, and the basement membrane was greatly thickened and appeared edematous.

It is apparent from the description, both gross and microscopic, that the patient had granulomatous lesions in which acid-fast bacilli were demonstrated and of which the histologic structure was consistent with a diagnosis of necrotizing tuberculosis. To reconstruct the exact clinical course of this patient is difficult. Apparently he had a first infection tuberculosis as evidenced by the calcified nodules in the x-ray film of the chest; he also had re-infection tuberculosis

as demonstrated at the autopsy by fibrous scars at both apices. About six months before entry, either the tuberculosis was reactivated from the fibrous scars or the patient acquired a new infection. The process went on for some time in reasonable equilibrium and the patient did not become critically ill until three to five weeks before his death. At that time the lesions took on another character; they became necrotizing in type, causing vascular spread and a rapidly fatal course.

There was no evidence in the sections of any additional disease such as sarcoidosis. All of the nodules that were observed were characteristic of tuberculosis.

Final Anatomical Diagnosis. Fibrous scars of the apices of the lungs; caseous and necrotizing tuberculosis of all lobes of the right lung; pleural effusion (right 1,500 cc., left 50 cc.); caseous and necrotizing tuberculosis of the tracheobronchial lymph nodes; necrotizing tubercles in the liver, porta-hepatic lymph nodes, spleen and right pleural surfaces; tuberculosis of skin with ulceration and secondary suppurative inflammation; localized areas of reddish discoloration of skin; desquamation of skin of trunk and extremities; "lymphoid tubercles" in the pleura-pericardium, and atrophy of the testis with focal hemorrhages.

Case Reports

Extensive Polycystic Disease of the Kidneys and Liver*

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POLYCYSTIC kidney disease has been extensively studied both in this country and abroad. It is reported to occur at autopsy approximately in the proportion of 1 to 500 cases. An exhaustive and excellent study of this condition was made by G. D. Oppenheimer in 1934,¹ and E. T. Bell² in 1935. Polycystic liver disease is less frequently encountered. A detailed study of this condition was made by L. Severi³ in 1937.

Polycystic disease is believed to be a congenital affection. Individuals afflicted with it usually develop gradually increasing renal insufficiency and die with the symptoms of uremia. Tetany has not been often mentioned as a complicating feature. The following case is of interest in this respect. It is also of interest because of the extensive involvement of the liver.

CASE REPORT

A forty-four year old housewife was admitted to the Lebanon Hospital to the service of Dr. David Greenberg on October 5, 1937, complaining of weakness, headache, vertigo, dragging sensation in the abdomen and nocturnal attacks of pain and spasm in the toes and fingers. The family history was essentially negative and outside of a herniorrhaphy four years ago, there were no previous illnesses. She was married and had four children; all four pregnancies and deliveries were normal and uneventful. There was amenorrhea for the past three months.

The patient was apparently well until about six months prior to admission when she began to experience the gradual onset of weakness, headache and dizziness. Three months prior

to admission she began to complain of being awakened at night with severe attacks of pain, spasm and cramps in the toes and fingers. She also felt a dragging heavy sensation in the abdomen, and complained of pyrosis, eructations, habitual constipation and "palpitation of the heart" with attacks of precordial pain. She lost no weight. There were occasional bouts of jaundice lasting from one to three days. Physical examination revealed slight jaundice, marked venous pulsations in the neck, systolic murmur over the base, blood pressure 118/80, a markedly enlarged liver which reached to the level of the umbilicus; the edge was hard and nodular but not tender; the spleen was enlarged, its edge was smooth and not tender.

Roentgen examination of the gastrointestinal tract disclosed an irregularity in the stomach which was interpreted as an organic lesion in the pars media of the stomach; x-ray of the chest was negative; x-ray of the genitourinary tract showed a large and ptosed right kidney; the left renal outline was visualized. Intravenous pyelogram revealed filling of the pelvis and calyces of the left kidney but there was an absence of the opaque media in the pelvis and calyces of the right kidney. During cystoscopy no urine could be obtained from the left side and the dye did not appear from either orifice in half an hour. The total phenolsulphonthalein excretion was 2 per cent. The specific gravity of the urine was fixed between 1.008 and 1.012 with an average daily output of 1,200 cc. It contained 1 plus albumin but no sugar. Microscopic examination showed occasional white and red blood cells. Blood count: red blood cells, 3,200,000; white blood cells 5,800; polymorphonuclears 72 per cent; lymphocytes 22 per cent; mononuclears 1 per cent; basophils 1 per cent; platelet count, coagulation and bleeding

* From the Laboratory of Lebanon Hospital, New York City, N. Y.

time were normal. The hemoglobin was 55 per cent (Sahli). Gastric analysis showed no free hydrochloric acid the total acidity being 10; there was no free hydrochloric acid after histamine injection. The basal metabolic rate was 0; stools were negative for occult blood. Blood chemistry findings are shown in Table 1. Temperature and pulse were always normal. Because of the x-ray findings in the stomach a diagnostic laparotomy was performed. The stomach was normal but the liver was found to be cystic. Biopsy of the liver showed congenital polycystic disease of the liver.

TABLE 1

	1st Admission	2nd Admission	3rd Admission
Non-protein nitrogen	120	204-162	255-300
Urea nitrogen	98	90	
Serum protein	5.2	8.5	6.7
Albumin	2.4	3.8	3.6
Globulin	2.8	4.7	3.1
A/G ratio86	.81	1.2
Icteric index	6	7	
Total cholesterol	155	194
Cholesterol esters	69	79
Phosphorus	9.5		
Phosphatase	2.1 (Bodansky)		
Calcium	8.4		

The postoperative course was uneventful and the patient was discharged with some improvement on November 23, 1937. She felt fairly well and had no complaints until May, 1938, when her symptoms of heartburn, vomiting, constipation and dizziness recurred. She was re-admitted to the hospital on June 4, 1938. At this time blood chemistry showed increased retention of nitrogenous waste products. (Table 1.) There was urobilin in the urine. The patient developed an infectious dermatitis during her stay in the hospital which was treated symptomatically. She showed some improvement; the non-protein nitrogen fell to 162 mg. per cent, and she was discharged on June 29, 1938.

She was re-admitted on September 22, 1938, with the symptoms of moderate uremia. She now was emaciated, the skin was bronzed and she appeared acutely ill. The liver edge was nodular and hard; its edge was felt at the level of the umbilicus. Both kidneys were palpable;

there was no ascites. On admission the hemoglobin was 45 per cent (Sahli); red blood cells 3,160,000; white blood cells 11,000; polymorphonuclears 80 per cent; lymphocytes 12 per cent; mononuclears 6 per cent; non-segmented polymorphonuclears 2 per cent. There was achromia, aniso- and poikilocytosis. The specific gravity of the urine was fixed between 1006 and 1008, and it contained 2 plus albumin and pus clumps. Blood chemistry showed increased retention of nitrogenous waste products. (Table 1.) The total non-protein nitrogen rose to 300 mg. per cent on September 28, 1938. The patient expired on October 6, 1938.

Autopsy: Only the kidneys and liver are described. Both kidneys were enlarged; their vertical diameters measured approximately 25 cm. Their surfaces were markedly irregular and were studded with variously sized cysts. The capsule stripped with moderate difficulty. (Figs. 1 and 2.) On section, the cut surfaces appeared irregularly honey-combed by the cross section of numerous variously sized cysts separated in most places by narrow strips of parenchyma or, in many places, only by their opposing walls. Most of the cysts contained a straw-colored serous fluid; some of the cysts contained a sanguineous turbid fluid, while still others were filled with a gelatinous homogeneous mass. The pelves were somewhat dilated, the ureters were patent. The microscopic appearance of the organ was that of variously sized cysts, many of which were markedly dilated. The smaller of these cysts were lined by low cuboidal epithelium which resembled that of collecting tubules, while the larger cysts were lined by a very markedly flattened epithelium. The cysts were filled with a pale pink staining amorphous material in which were seen red blood cells and cellular debris; other cysts, in addition, contained a purulent exudate. Among the cysts there were seen considerable areas of functioning kidney parenchyma. In these areas moderate numbers of fairly well preserved glomeruli were found which showed a mild degree of congestion, a moderately increased cellularity of the epithelium with beginning hyaline changes and edema. The tubules were irregular and most of them markedly dilated. Their epithelial walls were flattened and showed moderate to marked degrees of degenerative



FIG. 1. External surface of polycystic kidney. Note the closely packed cysts which vary in shape, size and depth.



FIG. 2. Cross section of polycystic kidney. Note the almost complete replacement of kidney tissue by the various sized cysts.



FIG. 3. Cross section of polycystic liver. Note the close resemblance to the cross section of the kidney.

changes. The interstitial connective tissue was markedly increased and, in most places, it was infiltrated by mononuclear cells. There was also a moderate degree of congestion present throughout. The blood vessels showed only minimal sclerotic changes; most of them appeared normal.

The liver weighed 4,200 Gm. and extended to about one finger above the umbilicus. The surfaces were irregularly nodular with cysts which varied in size from a few millimeters to 5 to 10 cm. in diameter. The diaphragmatic portion of the right lobe was the only part of the liver which was found to be relatively free of cysts. On section (Fig. 3) the cut surfaces resembled those of the kidneys and were also irregularly honey-combed by the cross sections of cysts most of which contained a clear serous fluid, while others contained a turbid brown fluid or a gelatinous homogeneous mass. In the

relatively uninvolved portions, the liver parenchyma presented a fairly normal appearance. The gallbladder and biliary tracts appeared normal. Microscopically, sections through the uninvolved portions showed normal liver architecture; there was a moderate degree of edema and the cytoplasm of the liver cells showed granular degeneration; the nuclei, however, were fairly well preserved. The portal fields seemed to be less prominent than seen normally. Sections taken from the cystic area showed numerous variously sized cystic cavities. The smaller of these were lined by low cuboidal epithelium resembling that of the bile ducts, while the larger cysts were lined by a markedly flattened epithelium. The cysts contained pale pink amorphous substance; there was no bile pigment seen in them. Some of these cysts were filled with a polymorphonuclear exudate and there was a similar infiltration in the adjacent

liver parenchyma surrounding them. The larger cysts were surrounded by a thickened fibrous wall. The liver tissue in between these cystic areas showed all grades of degenerative changes.

COMMENT

This case presented several noteworthy features. It is interesting to note that with such extensive involvement of both kidneys and liver this patient was able to lead a fairly normal existence up to a few months prior to her death. This ability to carry on in spite of these serious handicaps seems to depend upon two factors: First, the uninvolved portions of the kidneys and liver parenchyma undergo hypertrophy and partially compensate for the tissue destroyed by the cysts. This compensatory mechanism is especially marked in youth and early adult life. With advancing age, however, this ability is gradually decreased; the cysts on the other hand, continue to enlarge, gradually replacing the persistent islands of functioning tissue. As a result, the destruction of the latter goes on more rapidly than it can be replaced by compensatory hypertrophy and the patient progresses toward renal or liver insufficiency and death. The second factor in maintaining a normal existence is the ability of the organism to adjust itself and to acquire an increased tolerance to the accumulation of waste products in the blood. Another interesting feature of this case was the low blood pressure. Throughout the patient's stay in the hospital during the three admissions the blood pressure never rose above 118/80. This may be explained by the fact that the vessels of the kidney showed little or no sclerotic changes. It is now generally recognized that hypertension occurs in cases in which there is serious interference with the blood supply of the kidneys as shown by the well known experiments of Goldblatt⁴ who was able to produce hypertension in dogs by partially clamping the renal arteries.

The third feature of interest was the development of tetany. Symptoms of tetany have been observed to occur in cases of chronic nephritis. This is usually explained by the fact that due to the decreased ability of the kidney to excrete inorganic salts there is an accumulation of inorganic phosphates in the blood; with this the calcium is decreased since it has been shown that the relationship between these two elements tends to be reciprocal. The consequent development of hypocalcemia and the decrease in the serum calcium/phosphorus ratio is believed to play a significant rôle in the precipitation of clinical symptoms of tetany.⁵

The irregularity in the body of the stomach as revealed by x-ray was probably produced by pressure of the encroaching cysts of the left lobe of the liver upon the walls of the stomach. This was erroneously interpreted as a gastric neoplasm.

SUMMARY

1. A case of extensive polycystic disease of the kidneys and liver is reported in a forty-four-year old housewife.
2. There was no hypertension in spite of the extensive involvement of both kidneys.
3. The symptoms of tetany in this case were attributed to the increase of inorganic phosphates in the blood with a concomitant development of hypocalcemia and decrease in the serum Ca/P ratio.

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Mycotic Lung Infection*

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LUNG cysts are liable to infection. A case seeming to illustrate this is herein reported:

CASE REPORT

Mr. C. G. was admitted, at the age of fifty-five, to the Mount Morris Tuberculosis Hospital in May, 1937. He had been a glass cutter all his

the second rib and sixth dorsal spine. Breath sounds were roughened and crackling râles were audible above the clavicle and the fifth dorsal spine. On the left, an occasional râle was heard over the apex. X-ray films confirmed the clinic films. The patient was raising 3 to 4 ounces of odorless, mucopurulent sputum. A blood study revealed nothing except leucocytosis and cosino-

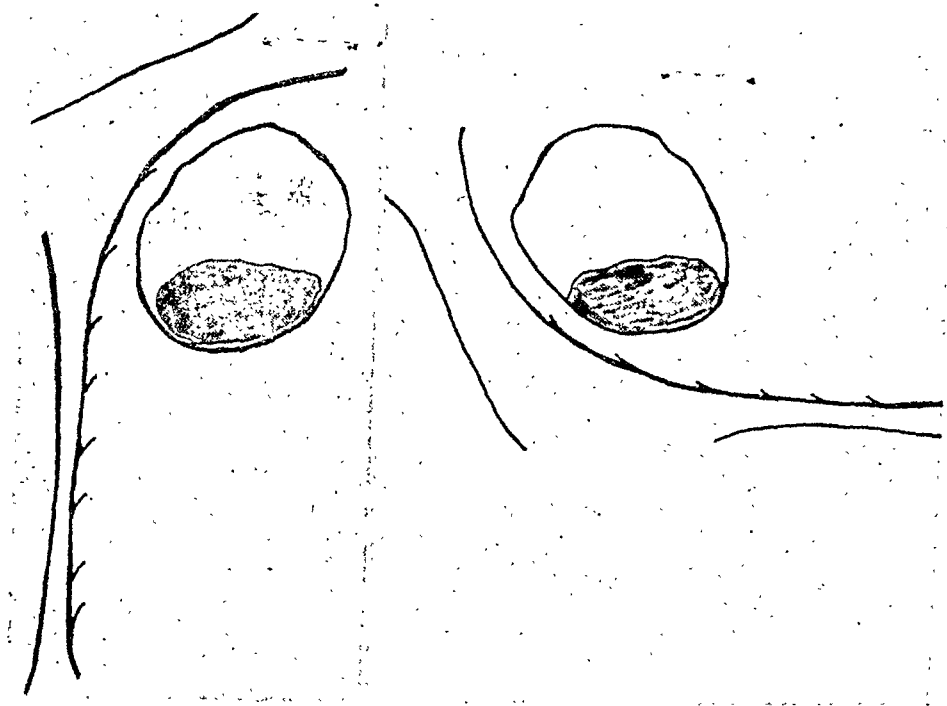


FIG. 1.

FIG. 2.

FIGS. 1 and 2. Sketches of the right apex in the erect anteroposterior (Fig. 1) and right lateral recumbent (Fig. 2) illustrating diagrammatically movement of the intracavitary mass with change in position.

life. The past history was non-contributory, except that he had "pleurisy" every year for the past ten years. In February, 1937, he contracted a cold, followed by a cough which became productive, and increasing weakness. X-ray in an itinerant clinic revealed a cavity at the right apex, with light infiltration at the left apex and he was admitted to this hospital.

Significant findings were limited to the chest, where on the right side there was dullness to

philia of 6 per cent, and sputum studies failed to reveal tubercle bacilli, fungi or Vincent's organisms. His temperature was subfebrile. The cough was paroxysmal and violent, especially when the patient was in the recumbent position. Bronchoscopy revealed inflammation of the right upper lobe bronchus.

X-ray films taken in January, 1938, in various positions revealed that there was a loose body in the cavity which shifted with change of

* From the Mt. Morris Tuberculosis Hospital, Division of Tuberculosis, New York State Department of Health.

position. This body was roughly circular, about 3 cm. in diameter, and could be seen to gravitate freely in a cavity three times as large. (Figs. 1 and 2.) On February 16, 1938, operation by a posterior approach disclosed an irregular cavity containing inspissated material having a mousy odor. This cavity had several bronchial communications. After adequate drainage, myoplasty was done to close the cavity and obliterate the bronchocutaneous fistulas. The patient was discharged from the hospital February 11, 1939, cured. Eosinophilia on discharge was 3 per cent.

A section of the thick cavity wall revealed "a zone of fibrotic tissue with marked necrosis of the inner layer. All layers are infiltrated with eosinophils." Neither yeast, molds, fungi nor tubercle bacilli were seen.

The cavity contents were shown by microscopic examination to be mycotic material of the aspergillus group. Attempts were made to identify the organism more definitely but all cultures failed to grow.

Follow-up on November 7, 1944, revealed that the patient has been working as a glass cutter and is apparently well.

COMMENTS

The occupational history of glass cutting, involving the use of carborundum and pulverized sand, for forty years, confused the picture, as did the presence of some infiltration at the left apex, interpreted as being tuberculosis. The exact mechanism involved in the condition described is obscure. It is suggested that there was a lung cyst or emphysematous bleb at the right apex. This sustained an aspergillus infection, which then died, leaving a thick-walled cavity containing a mobile, putty-like mass of dead organisms. This mass sometimes acted as a ball-valve over the bronchial fistulas causing the severe paroxysmal cough.

Venous Catheterization

ADVANCES in medicine depend on the development of new methods. It is easy to think of things that one would like to know. It is more difficult to outline a problem for which methodology to give the needed information is available. Interest in cardiovascular research has been greatly stimulated by the demonstration of South American investigator¹ and by the group at Bellevue Hospital that a radio-paque catheter can be safely introduced into the venous system through an incision in a superficial vein.^{2,3} Once in the vein, the catheter may be guided under the fluoroscope into the jugular vein, the right atrium, the right ventricle or the pulmonary artery. It may be passed down through the right atrium into the inferior vena cava and on out into the hepatic or renal veins. In patients with atrial septal defect, the catheter may enter the left side of the heart. In patients with a ventricular septal defect, the catheter may be passed into the aorta.

This method has had immediate clinical application in the diagnosis of certain types of heart disease. High right ventricular pressure is present in patients with cor pulmonale.⁴ The presence of certain types of shunts can be demonstrated by study of the oxygen content of samples of blood drawn from different chambers of the

heart.^{5,6} These diagnostic methods are of great interest because of the recent advances in cardiac surgery.

Venous catheterization has opened a wide field of investigation in the field of cardiac dynamics. The lesser circulation can now be studied and many questions concerning the control of blood flow through the lungs will be answered in the near future. The data obtained on the relations between atrial pressure and ventricular filling will lead to a better understanding of the factors controlling the cardiac output.

A method for measuring the hepatic blood flow using the technic of hepatic vein catheterization has recently been described.⁷ Studies on the metabolism of the kidney are now possible as methods are available for obtaining both the renal blood flow and the renal arteriovenous oxygen difference.⁸

At least 1,500 persons have been subjected to this procedure in the last four years. Thrombosis at the site of the incision in the antecubital vein occurs occasionally. There have been no serious complications. It seems safe to predict that venous catheterization will become an accepted technic in many hospitals.

EUGENE A. STEAD, JR., M.D.

¹ PADILLA, T., COSSIO P. and BERCONSKY, I. Sondeo del corazón. *Semana méd.*, 2: 391, 445 and 645, 1932.

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Book Review

THIS small, inexpensive volume,* "A Primer for Diabetic Patients," contains a surprising amount of practical information for the diabetic patient which should lead to his informed cooperation in management.

The first five chapters contain brief simple discussions of diabetes, the urine tests, the insulins, the complications of diabetes and their remedies. The last four chapters, comprising more than half the book, are devoted to foods and diets and are sufficiently detailed to permit anyone of average intelligence to plan palatable menus of known composition. Questions at the end of each chapter are designed to emphasize the important points covered.

* A PRIMER FOR DIABETIC PATIENTS. By Russell M. Wilder, M.D., PH.D., F.A.C.P. Eighth edition reset. Cloth. Pp. 192 with 8 illustrations. Philadelphia, 1946. W. B. Saunders Company. Price \$1.75.

While the value of the "Primer" is undisputed, and its popularity attested to by the number of editions published, certain minor criticisms may perhaps be ventured. The insistence that in general not more than twenty units of protamine zinc insulin should be used in one day seems a trifle conservative. Perhaps more stress is placed on weighing foods and learning their substitution value in a standard diet than teaching their composition and actual caloric equivalents. The height-weight-age tables at the back of the book are in type so small as to be difficult to read.

However, these are hardly serious objections. Otherwise, the clarity and detail of the presentation, the excellence of the typography and the handy pocket-sized format make the "Primer" prescribed reading for every diabetic.

F. K. H.

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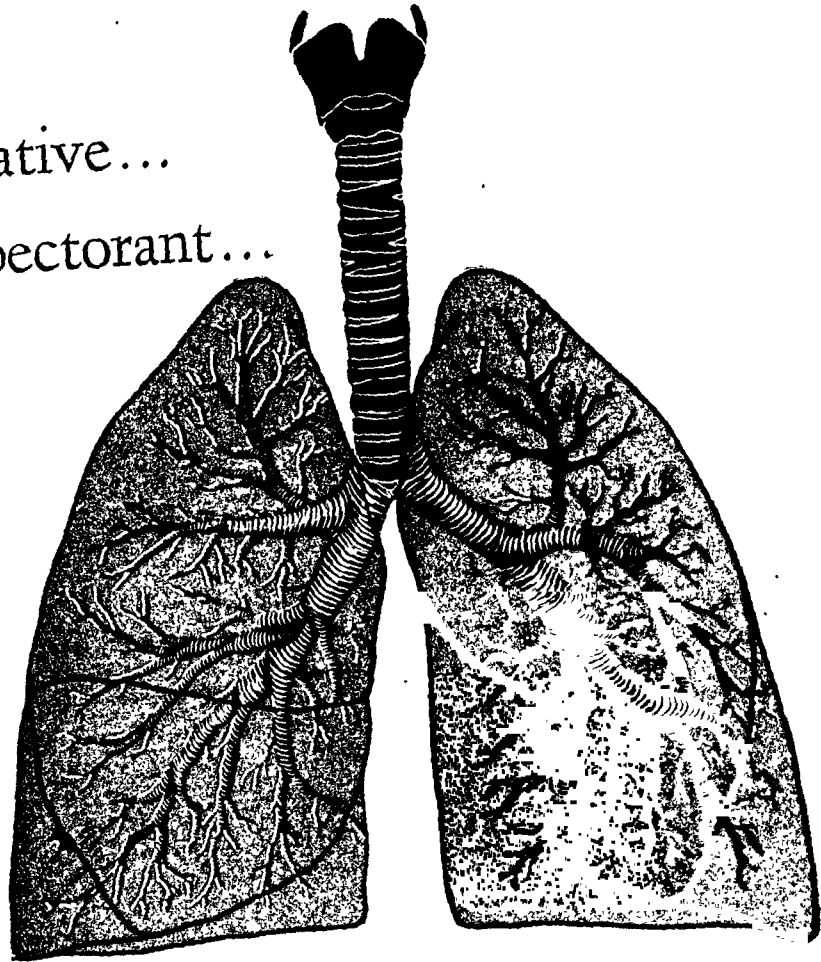
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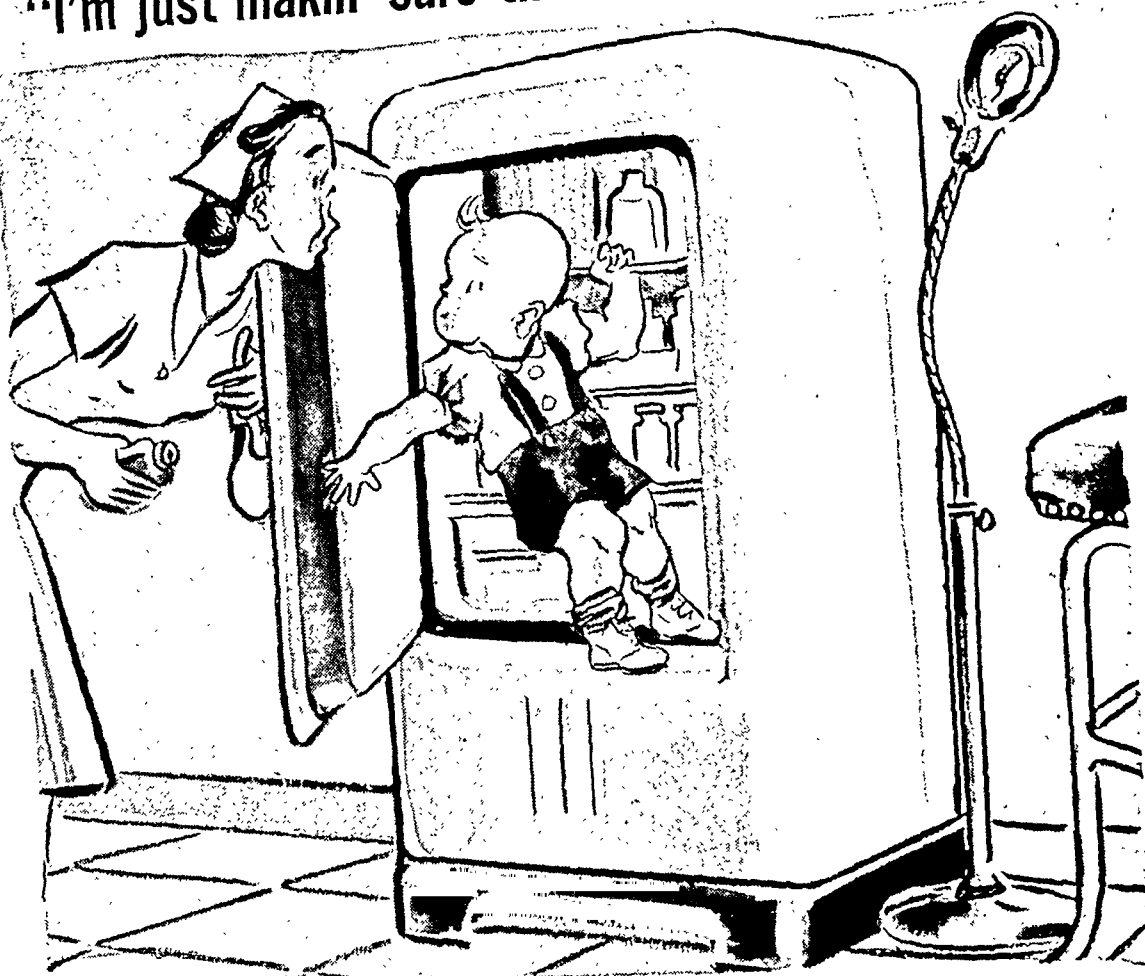
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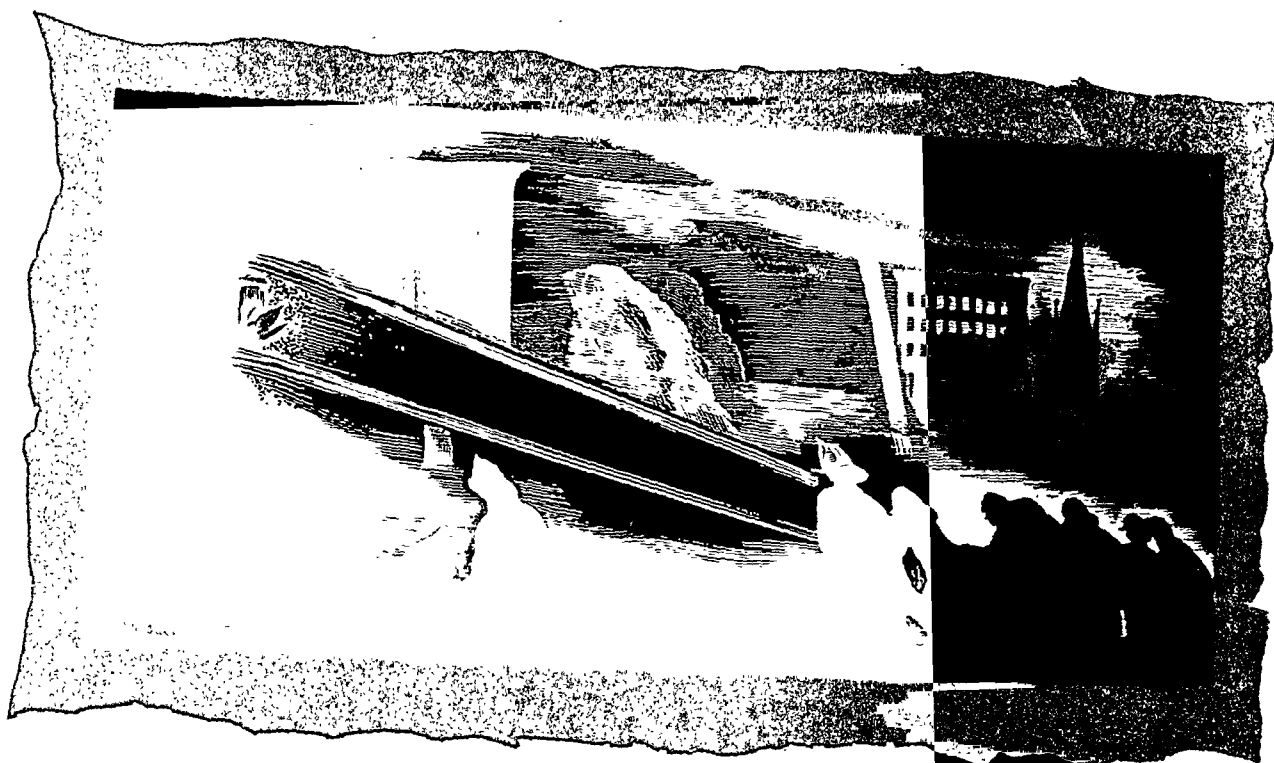
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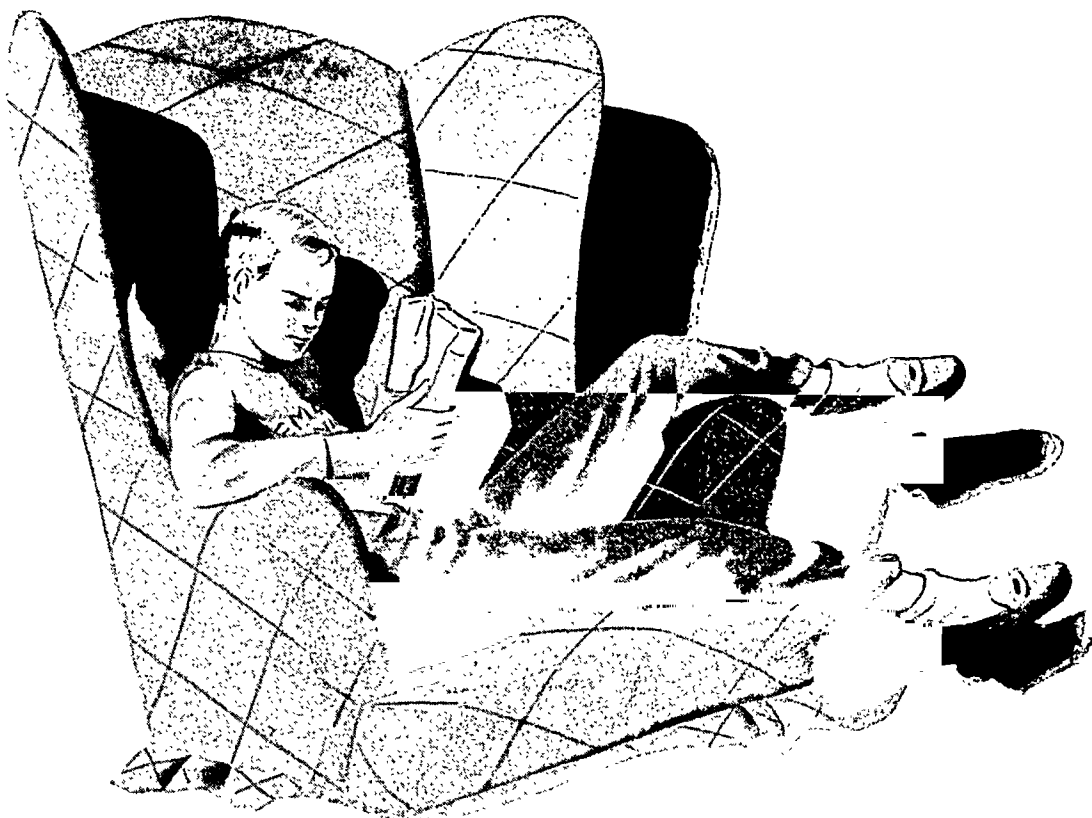
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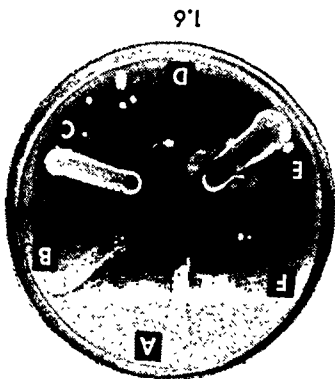
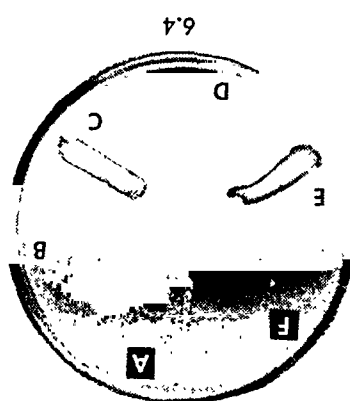
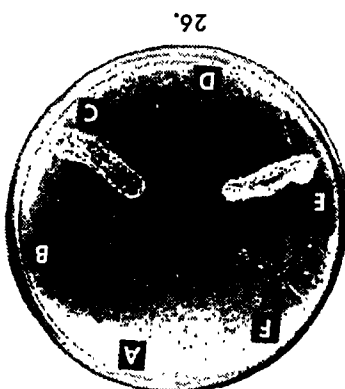
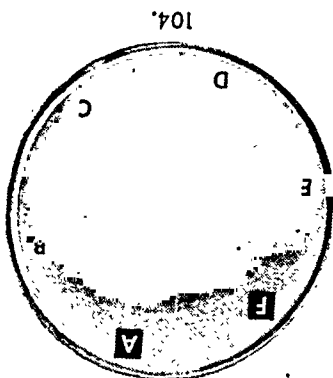
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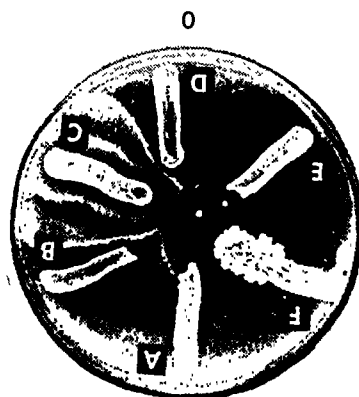
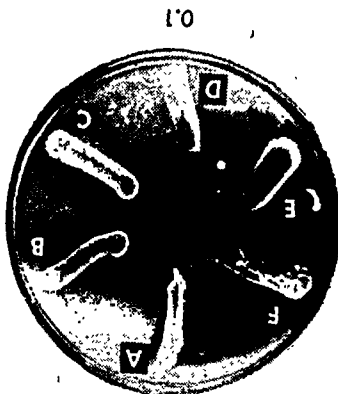
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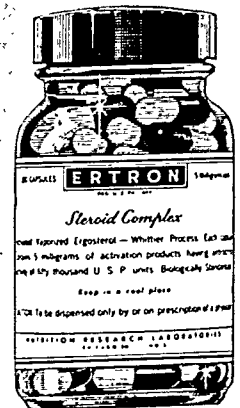
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Levels of Blood Pressure in Both Arms and Legs in Normal Subjects and Patients Suffering from Certain Diseases*

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WHEN studies of the circulation in coarctation of the aorta first were undertaken in this clinic, we were unable to find in the literature adequate data relating to blood pressure values in all four extremities for comparison. During the course of these studies, measurements were made of the blood pressure in both upper and lower extremities of normal subjects and patients with cardiovascular and other disease states. These data form the basis of this report. It seemed appropriate to record these data since no other reports are available in which the blood pressure in the four extremities are recorded.

Before 1924, it was the prevailing opinion that no blood pressure difference existed between upper and lower extremities in normal human subjects. Some of the earliest studies in which blood pressures were taken in both arms and legs were made on cases of aortic regurgitation. Hill and his associates,^{1,2} in 1909 and 1912, first demonstrated that in aortic regurgitation systolic pressures were uniformly higher in the leg than in the arm, a finding so constant that they considered it of diagnostic value. This was confirmed by Murray³ in 1914 in nineteen cases of aortic insufficiency, in whom the average systolic thigh pressure exceeded the

upper arm by 26 mm. The observations of Williamson⁴ in 1921 in twenty-four patients with aortic incompetence showed a difference in the arm and leg readings in favor of a higher leg pressure in only fourteen patients. He concluded that the difference was largely due to arterial thickening. The investigations of Bazett⁵ in 1924 demonstrated in dogs a higher systolic pressure in the femoral than in the brachial artery. Burdick and his associates in 1925,⁶ using photographic methods for the simultaneous registration of systolic blood pressures in arm and thigh, found the systolic pressure in normal subjects constantly higher in the leg than in the arm. In a horizontal resting position, the average difference was 38 mm. higher in the thigh, and increased to 68 mm. with exercise. In 1929, Strang,⁷ from a study of fifty-four normal subjects, observed blood pressure readings in the leg in all instances higher than in the arm, regardless of position, with an average difference of 33 mm. of mercury. Hamilton and others⁸ in 1939 reported the blood pressure higher in the legs than in the arms in thirty subjects, and Cady⁹ in the same year observed higher systolic pressures in the popliteal than in the brachial artery, the difference being most marked in hypertensive cases.

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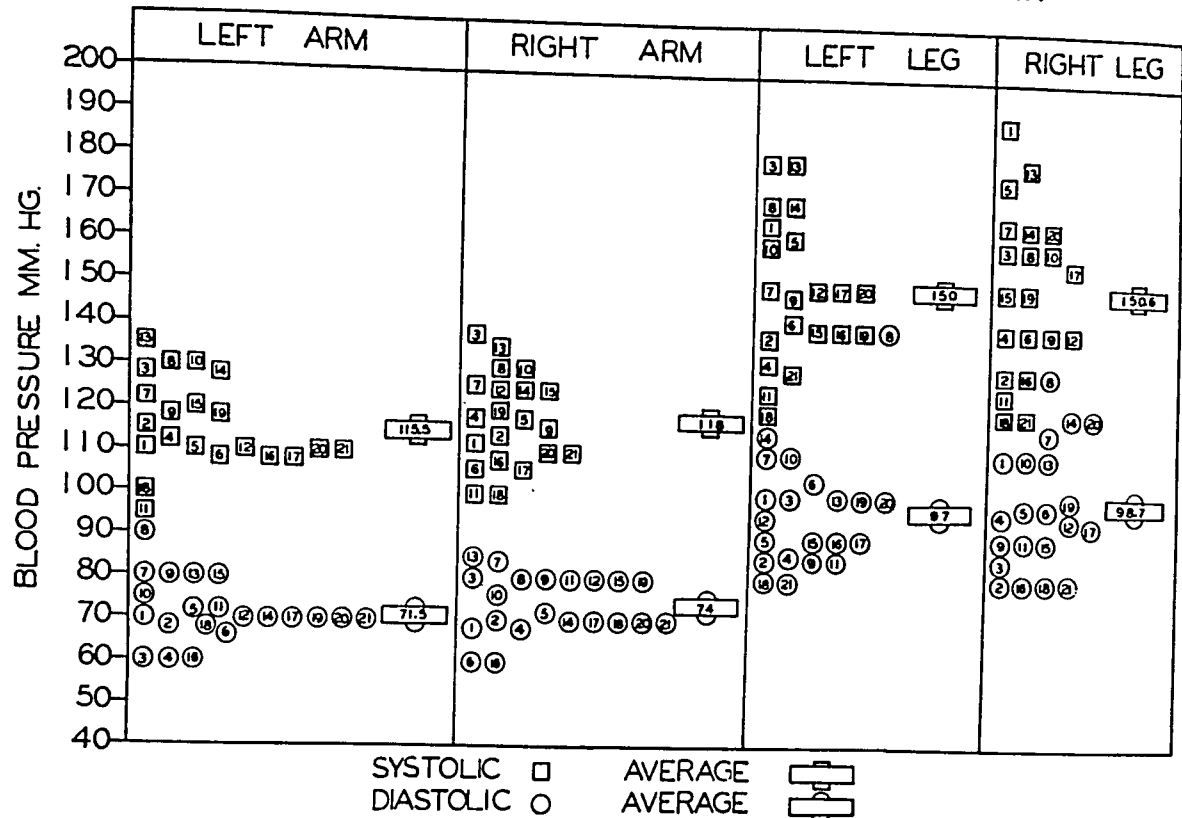


FIG. 1. In this figure are shown the measurements of blood pressure in the upper and lower extremities of twenty-one normal subjects, with average values for each extremity. In this illustration, as well as in Figures 2 to 8 inclusive, appropriate symbols identify systolic and diastolic levels and the average for the group. The numbers in each circle and square identify each patient. The average blood pressure for each extremity is recorded with the symbol for the average.

A study of the blood pressure in the lower extremity was made in 1943 by Wendkos and Rossman¹⁰ in 500 soldiers between the ages of eighteen and thirty-five who had normal cardiovascular systems. They excluded those subjects in whom the blood pressure in the arm registered over 140 mm. systolic or 90 mm. diastolic. All pressures were recorded with the subject supine. In all cases the systolic blood pressure in the thigh (average 154.8 mm.) was greater than the corresponding blood pressure in the arm (average, 118.3 mm.) and the diastolic blood pressure in the thigh (average, 91.9 mm.) was either equal to or greater than the corresponding blood pressure in the arm (average, 70.6 mm.). The average difference in systolic blood pressure between arm and thigh was 36.5 mm., and the average diastolic difference 21.4 mm. Height of the subject did not appear to influence the average blood pressure in the thigh, al-

though an increase in weight was associated with an increase in blood pressure in the lower extremity.

Gambill and Hines,¹¹ in 1944, studied blood pressures in the four extremities of 112 subjects with a wide variety of clinical states, but without significant vascular disease. They obtained an average systolic value in the arm of 115 mm. and in the thigh of 150 mm., with an average differential blood pressure of 35 mm. The diastolic blood pressure averaged 27 mm. higher in the thigh. The systolic blood pressure in the lower extremity showed the greatest tendency to vary from the average. The blood pressure averaged slightly higher in the right thigh than in the left.

Bazett⁵ showed that the difference in systolic pressures in femoral and carotid arteries was exaggerated when aortic regurgitation was experimentally produced. In 1944, Kotte, Iglauer and McGuire¹²

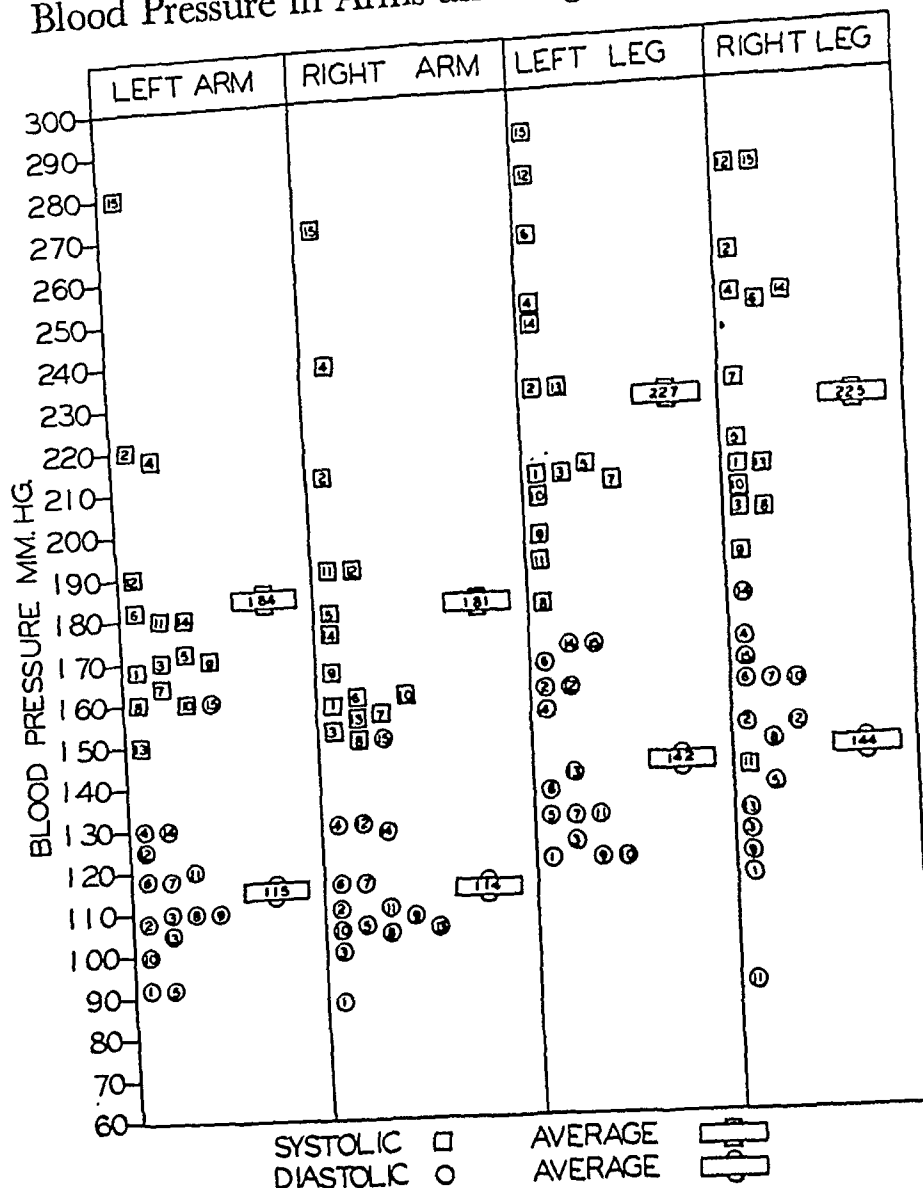


FIG. 2. In this figure the measurements of blood pressure are shown in the upper and lower extremities of fifteen cases of hypertension, with average values for each extremity.

measured the blood pressure in subjects with normal blood pressure, hypertension and aortic insufficiency, using the cuff method as well as an optical manometer. They found the femoral systolic pressure more frequently elevated in cases of aortic regurgitation, with differences usually greater than in hypertensive or "normotensive" groups.

Taussig,¹³ in 1916, investigated blood pressures in patients with exophthalmic goiter, and found both systolic and pulse pressures in the leg substantially higher than in the arm. The differential systolic pressure averaged 37.3 mm. and the diastolic 7.6

mm. higher in the leg. The blood pressure differences in exophthalmic goiter were considered of the same type as in aortic regurgitation though of less degree.

The excellent collection of cases of coarctation of the aorta by King¹⁴ in 1937 includes fifty-six adults in whom blood pressure measurements were recorded in all four extremities. The systolic pressures averaged 67 mm. higher in the upper extremity than in the leg. In twelve typical cases of coarctation, King found that ten had an absolute hypertension in the arms; in only one case was it normal. Steele¹⁵ noted the frequent elevation of diastolic

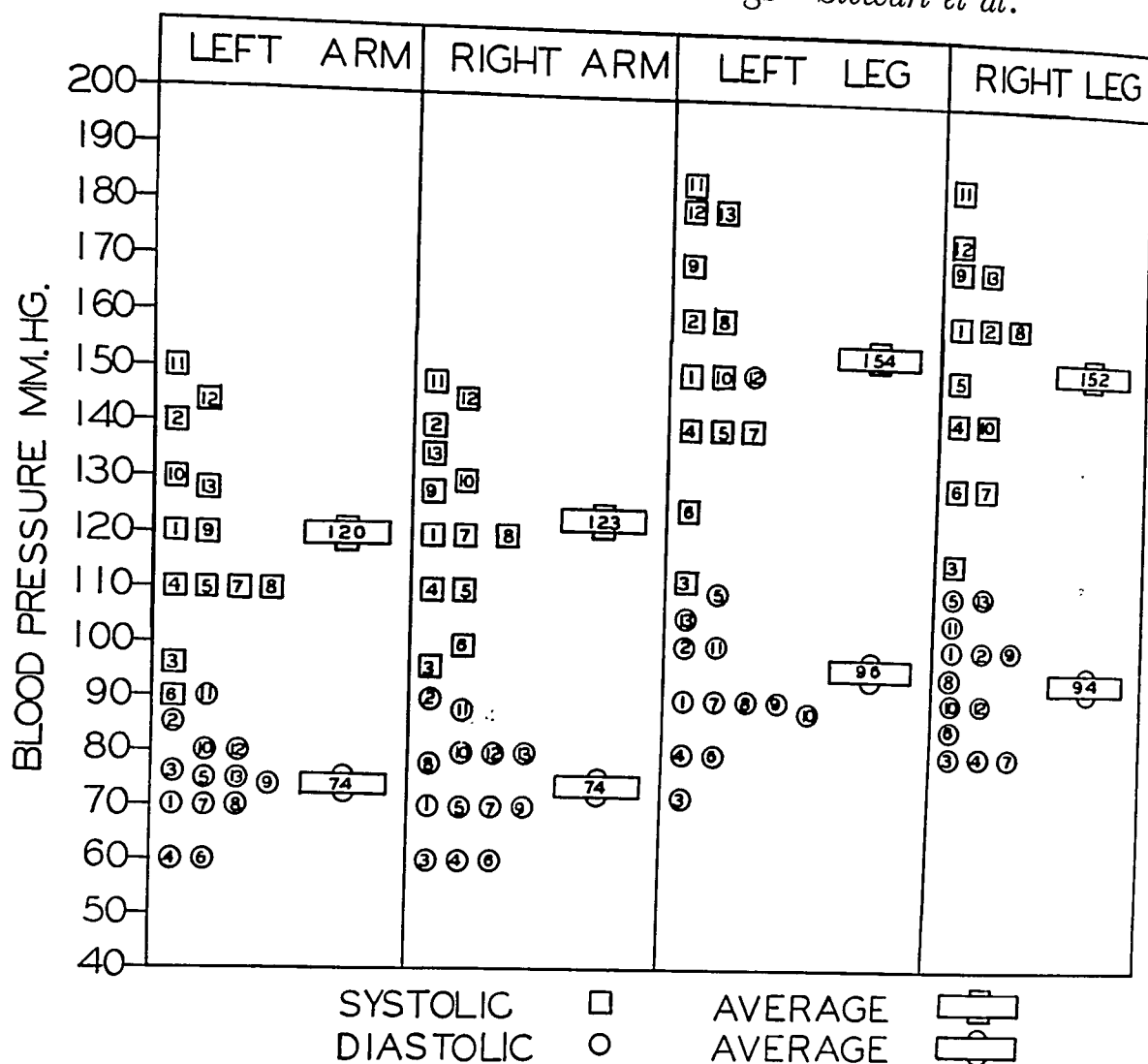


FIG. 3. In this figure the measurements of blood pressure are shown in the upper and lower extremities of thirteen patients with rheumatic heart disease, having mitral stenosis and insufficiency, but without involvement of the aortic valve. Average values are given for each extremity.

pressure in the legs, often approximating that of the arms in cases of coarctation of the aorta, and postulated an increase in peripheral arteriolar tone similar to that in essential hypertension. In fourteen cases studied by Stewart and Bailey¹⁶ in 1941, all but one showed a higher systolic pressure in the arms than in the legs, and of eleven patients, three had higher diastolic pressures in the legs, four approximately equal diastolic pressure in the arms and legs, and three exhibited a higher diastolic pressure in the arms. In studying peripheral blood flow in cases of coarctation, Stewart, Haskell and Evans¹⁷ found the blood pressure in the arms considerably higher than in the lower extremities, obtaining readings as high as

200/100 mm. in the right arm. They also observed wider pulse pressures in the upper extremities than in the legs.

OBSERVATIONS

Measurements of blood pressure were made in all four extremities of 123 subjects ranging in age from eleven to seventy years.* All observations were made under basal conditions. Before readings were taken the subjects were kept at rest in a horizontal position for at least one-half hour in a room with constant temperature and humidity. A standard 5-inch blood-pressure cuff connected to a mercury manometer

* All blood pressure measurements were taken by H. J. Stewart and W. F. Evans.

Blood Pressure in Arms and Legs—*Stewart et al.*

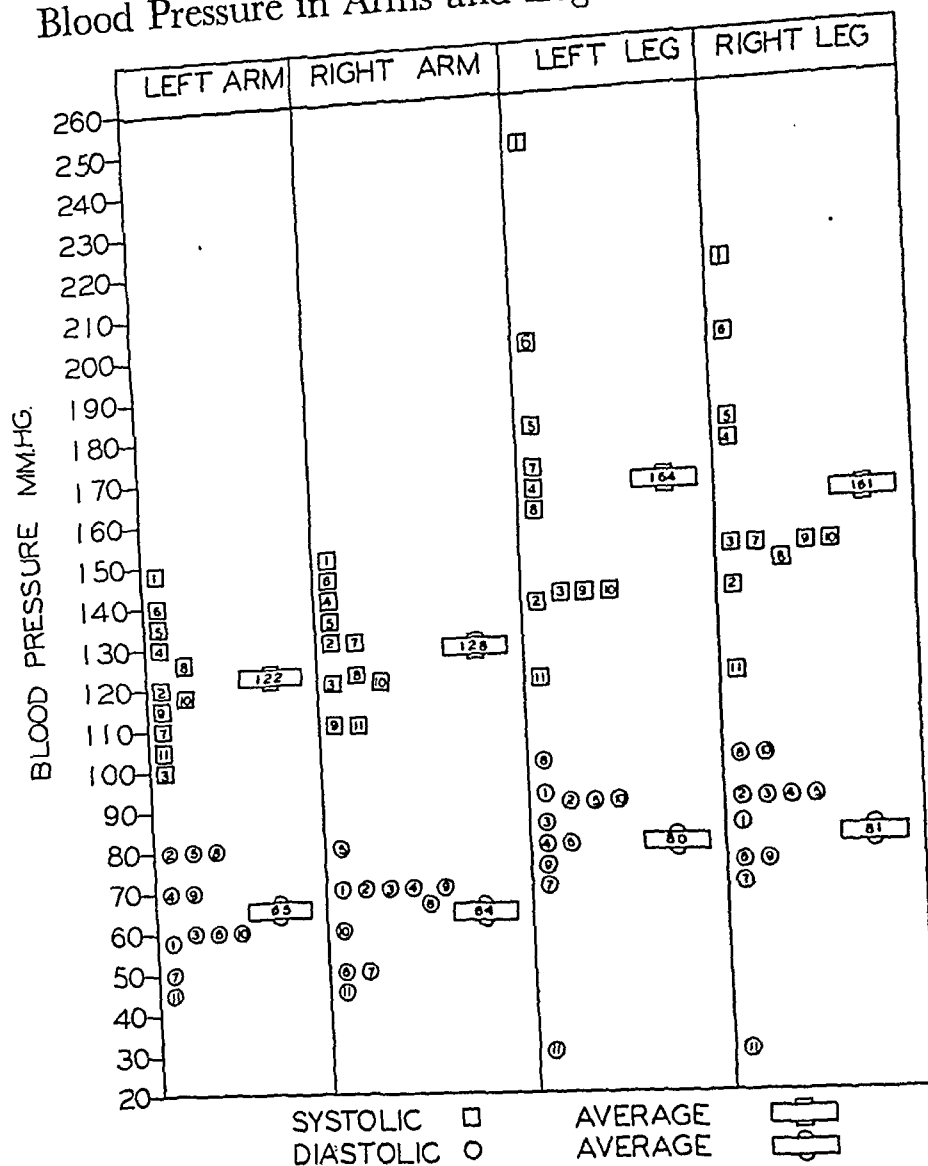


FIG. 4. In this figure the measurements of blood pressure are shown in the upper and lower extremities of eleven patients with rheumatic heart disease, having mitral stenosis and insufficiency and also aortic insufficiency. The patients in cases 3, 5, 6 and 11 had aortic stenosis as well. Average values are given for each extremity.

was used for both the arm and the thigh. Ballooning and displacement of the cuff was prevented by wrapping a towel securely around it. The pulse rate was recorded, and blood pressure readings were taken in the horizontal position. The level at which the first sound appeared was taken as the systolic pressure, and the point at which the sounds became suddenly muffled or disappeared was regarded as the diastolic pressure, as recommended by the American Heart Association.¹⁸ In taking the blood pressure in the legs in patients with coarctation of the aorta, these changes may be

heard for only a few beats. In a number of instances several readings were made, the last was then usually taken as representing the most accurate figure.

Observations were made on twenty-one normal subjects, fifteen patients with hypertension, twenty-three patients with coarctation of the aorta, thirteen patients suffering from rheumatic heart disease with mitral stenosis and insufficiency, eleven patients exhibiting rheumatic heart disease with mitral stenosis and insufficiency and also aortic insufficiency (including five patients who also had aortic stenosis) eleven subjects

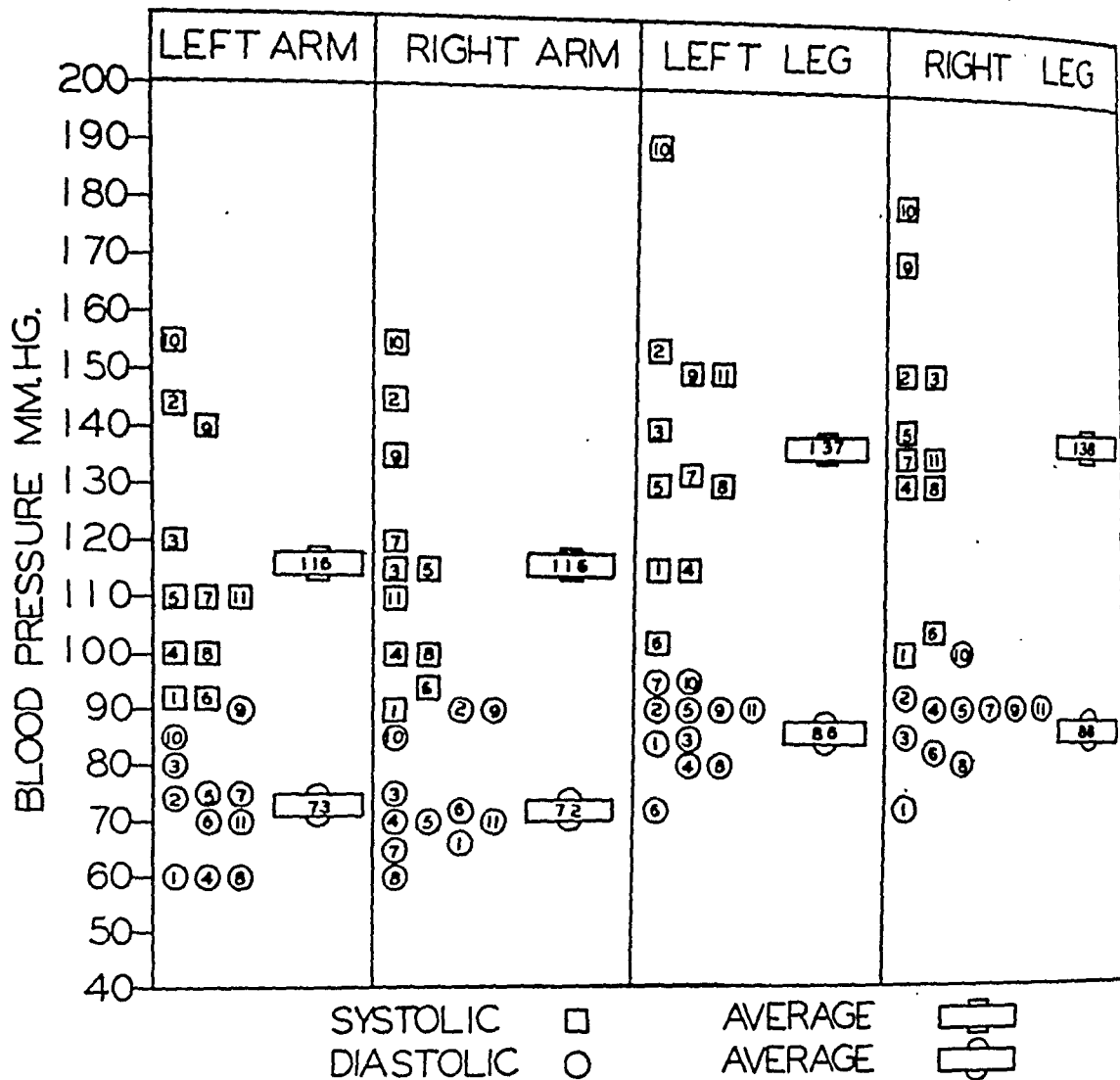


FIG. 5. In this figure the measurements of blood pressure are shown in the upper and lower extremities of eleven patients having congenital heart disease, with average values for each extremity. The patient in Case 1 suffered from pulmonary stenosis with interventricular septal defect, in Case 3 from pulmonary stenosis, in Case 4 from patent ductus arteriosus or foramen ovale, in Cases 2, 5, 6, 7, 8, 9 and 10 from interventricular septal defect.

with congenital heart disease, ten patients with Graves's disease and nineteen patients exhibiting a variety of other diseases.

The blood pressure of the four extremities for all patients in each group, as well as the averages for the group are shown in Figures 1 to 8 inclusive. In Figure 9 the average blood pressure values in each extremity are shown for all rubrics.

Normal Subjects. The measurements of blood pressure in the upper and lower extremities of twenty-one normal subjects are shown in Figure 1. The ages ranged from nineteen to twenty-seven, except patients number 10 and 21 who were forty-six and fifteen years of age, respectively. In the left

arm a systolic range of 95 to 135 mm., with an average of 115.5 mm., and in the right arm a systolic range of 100 to 138 mm. with an average of 118 mm., were obtained. The diastolic pressure in the left arm ranged from 60 to 90 mm., averaging 71.5 mm.; in the right arm it ranged from 60 to 84 mm., averaging 74 mm. In the left lower extremity the systolic pressure ranged between 120 and 180 mm., averaging 150 mm., and in the right lower extremity it ranged between 120 and 190 mm., averaging 150.6 mm. The diastolic pressures in the legs were similarly elevated, in the left leg ranging from 80 to 140 mm., averaging 97 mm., in the right leg ranging from 80

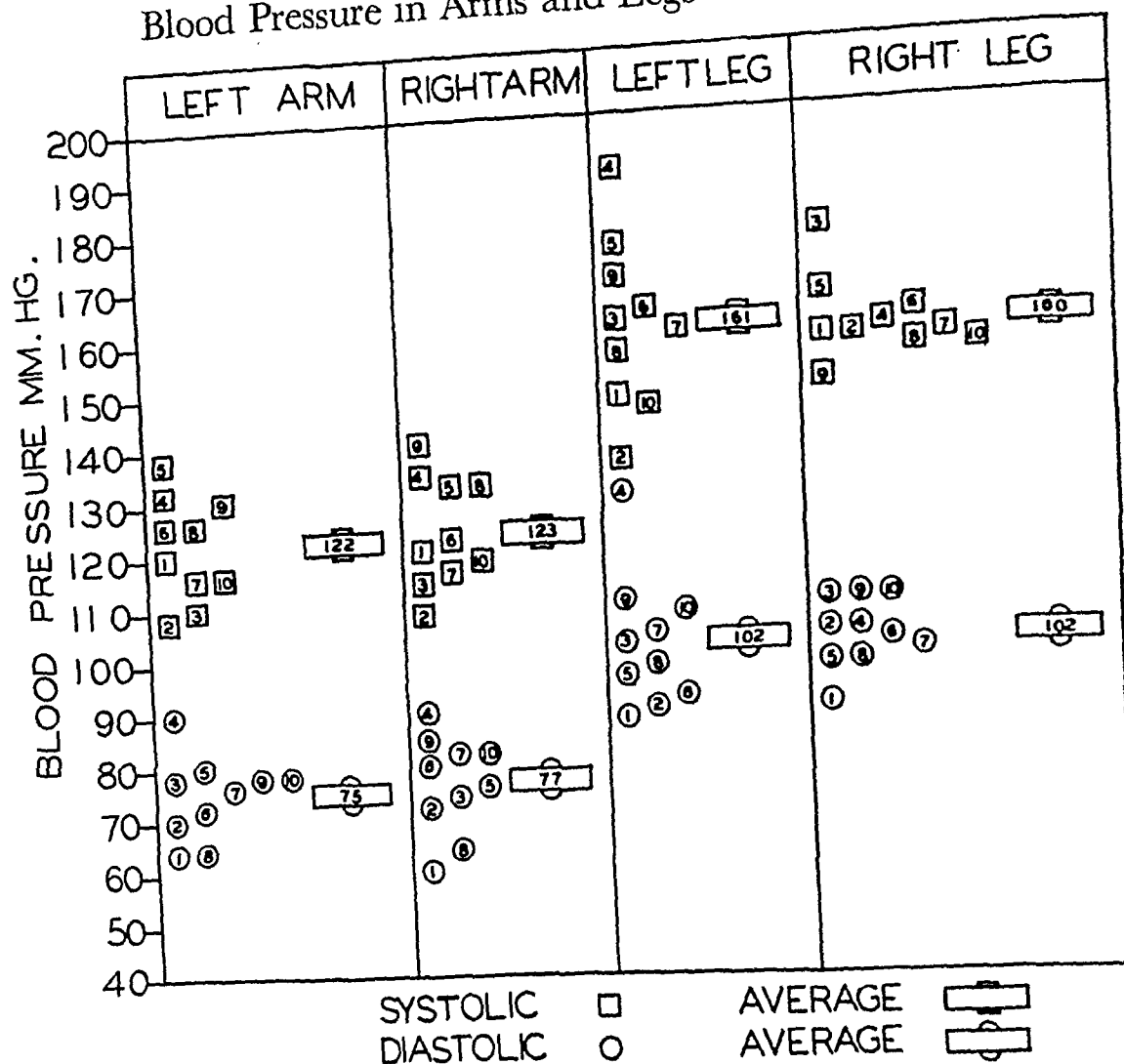


FIG. 6. In this figure the measurements of blood pressure are shown in the upper and lower extremities of ten patients with Graves's disease, with average values for each extremity.

to 130 mm., averaging 98.7 mm. Both the systolic and diastolic blood pressure in the legs were higher than those in the arms in every patient. Average blood pressures in both right extremities were higher than in the left.

Hypertensive Patients. In Figure 2 the blood pressure values, with averages, are plotted for each extremity in fifteen cases of hypertension. In the left arm a systolic range of 150 to 280 mm., with an average of 184 mm., and in the right arm a systolic range of 150 to 270 mm., with an average of 181 mm. were obtained. The diastolic pressure in the left arm ranged from 92 to 160 mm., averaging 115 mm., in the right arm it ranged from 88 to 150 mm., averaging 114 mm. In the left thigh, the systolic pressure ranged between 180 and 290 mm.,

averaging 227 mm., and in the right thigh it ranged between 140 and 280 mm., averaging 225 mm. The diastolic pressures in the left lower extremity fell in a range between 120 and 170 mm. with an average of 142 mm., in the right lower extremity the value ranged between 90 and 180 mm., averaging 144 mm. Systolic and diastolic blood pressures in the legs were higher than in the arms in the cases of hypertension.

Patients with rheumatic heart disease were separated into two groups, namely, those exhibiting mitral stenosis and insufficiency but without involvement of the aortic valve, and those with mitral valve lesions together with involvement of the aortic valve.

Rheumatic Heart Disease without Aortic Insufficiency. In Figure 3 the blood pressure

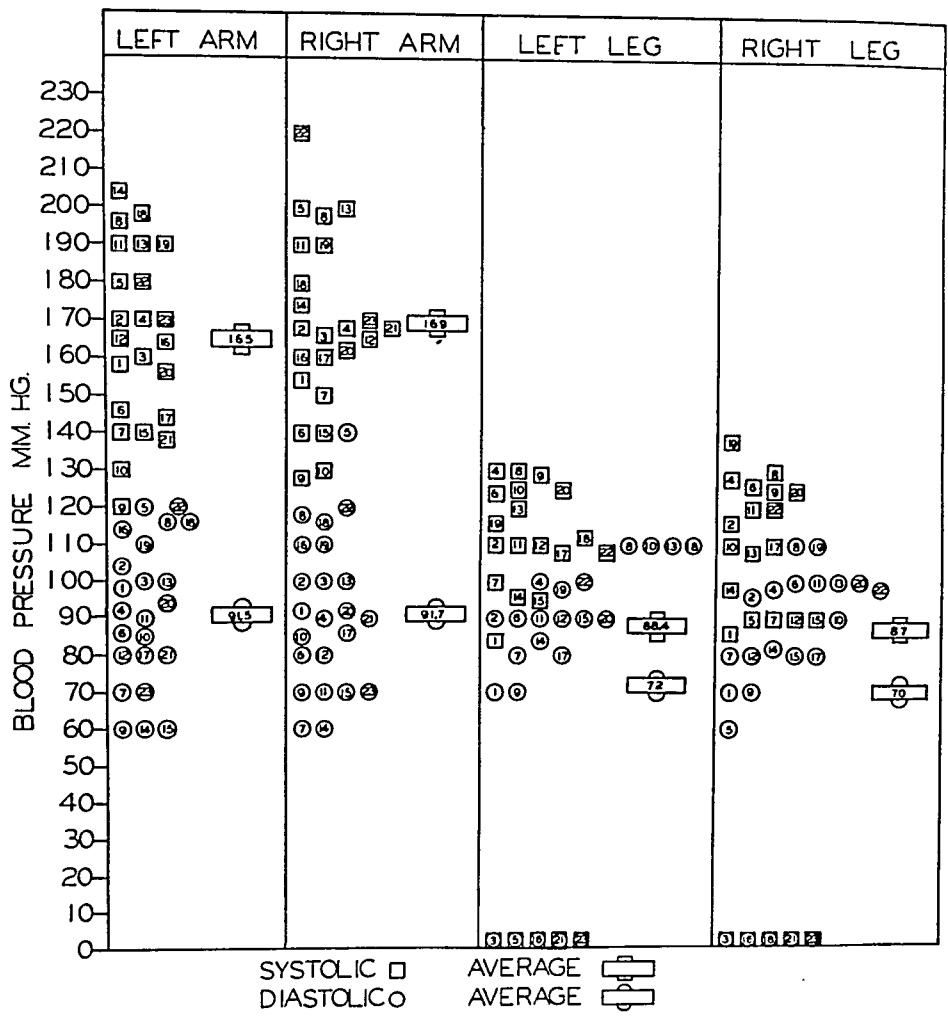


FIG. 7. In this figure the measurements of blood pressure are shown in the upper and lower extremities of twenty-three patients exhibiting coarctation of the aorta, with average values for each extremity.

readings are shown for thirteen cases with mitral disease without aortic involvement. Systolic pressures ranged from 90 to 150 mm., averaging 120 mm. in the left arm, and from 96 to 150 mm., averaging 123 mm., in the right arm. Diastolic pressures ranged from 60 to 90 mm., averaging 74 mm. in both arms. In the left lower extremity, systolic pressures ranged from 114 to 185 mm., averaging 154 mm. In the right lower extremity they ranged from 116 to 185 mm., averaging 152 mm. The diastolic pressures in the left leg ranged between 72 and 150 mm., with an average of 96 mm., and in the right leg diastolic pressures ranged from 80 to 110 mm., with an average of 94 mm. In short, in patients with rheumatic heart disease with mitral valve lesions only, higher systolic and diastolic

blood pressures were obtained in the lower than in the upper extremity.

Rheumatic Heart Disease with Aortic Insufficiency. In Figure 4 the data relating to eleven patients with mitral stenosis and insufficiency, and aortic insufficiency of rheumatic etiology are shown. Four of the eleven patients also had aortic stenosis; these cases are indicated in the legend. In the left arm, the systolic range was from 100 to 148 mm., averaging 122 mm., in the right arm the range was from 110 to 150 mm., averaging 128 mm. The diastolic range in the left arm was 45 to 80 mm., with an average of 65 mm., in the right arm 45 to 80 mm., with an average of 64 mm. The systolic pressures in the left leg fell in a wide range between 120 and 248 mm., with an average of 164 mm.; in the right leg systolic pressures

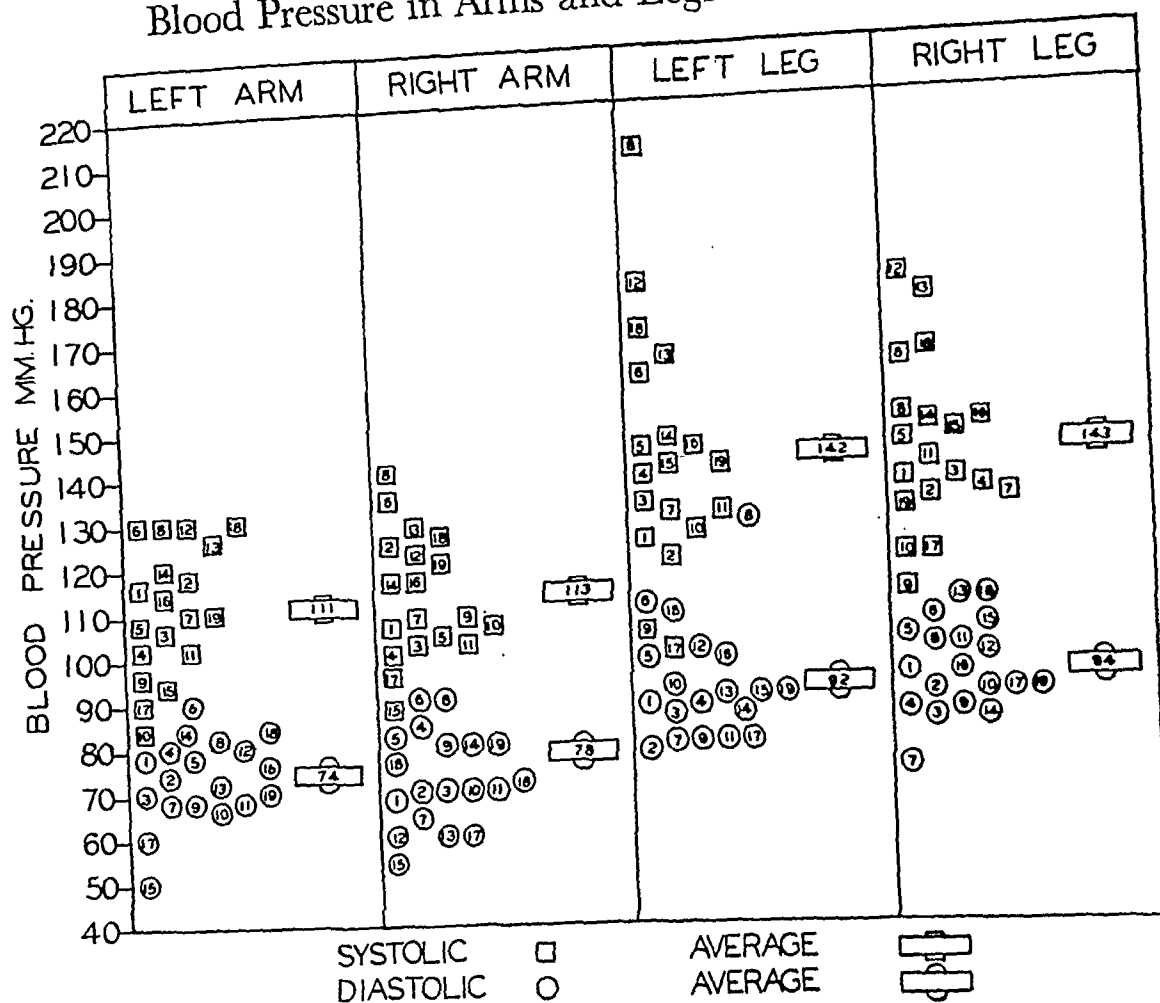


FIG. 8. In this figure the measurements of blood pressure are shown in the upper and lower extremities of nineteen miscellaneous patients having the following diseases: Patient No. 1 suffered from chronic constrictive pericarditis, No. 2 from suppurative arthritis, No. 3 from gastritis, No. 4 from disseminated lupus erythematosus, No. 5 from diabetes mellitus, No. 6 from sciatica, No. 7 from congenital syphilis, No. 8 from generalized arteriosclerosis, No. 9 from arteriosclerosis, No. 10 from carcinoma of the lung, No. 11 from Hodgkin's disease, No. 12 from diabetes mellitus, No. 13 from bronchiectasis, No. 14 from adrenal tumor (p. p.), No. 15 from myxedema, No. 16 from beriberi, No. 17 from chronic constrictive pericarditis, No. 18 from Raynaud's disease, and No. 19 from chronic constrictive pericarditis.

ranged from 120 to 218 mm., averaging 161 mm. Diastolic pressures in both lower extremities ranged from a low value of 30 mm. to 100 mm., averaging 80 mm. in the left leg and 81 mm. in the right leg. It appears, therefore, that in patients with mitral valve lesions and also aortic insufficiency of rheumatic origin, systolic and diastolic blood pressures in the legs are higher than in the arms, and average pulse pressure differences are wider than in cases with mitral valve lesions alone.

Congenital Heart Disease. Data relating to eleven patients suffering from congenital heart disease exclusive of coarctation of the

aorta are shown in Figure 5. The diagnoses in each patient are shown in the legend. Septal defects were most common. They suffered from the following defects: Tetralogy of Fallot, pulmonary stenosis, patent foramen ovale, and interventricular septal defects. In the left arm the systolic pressure ranged between 92 and 155 mm., averaging 116 mm., and in the right arm between 90 and 155 mm., averaging 116 mm. The diastolic pressure in both arms ranged from 60 to 90 mm., averaging 73 mm. on the left and 72 mm. on the right. In the left leg systolic pressures fell in a range from 102 to 190 mm., averaging 137 mm., and in the

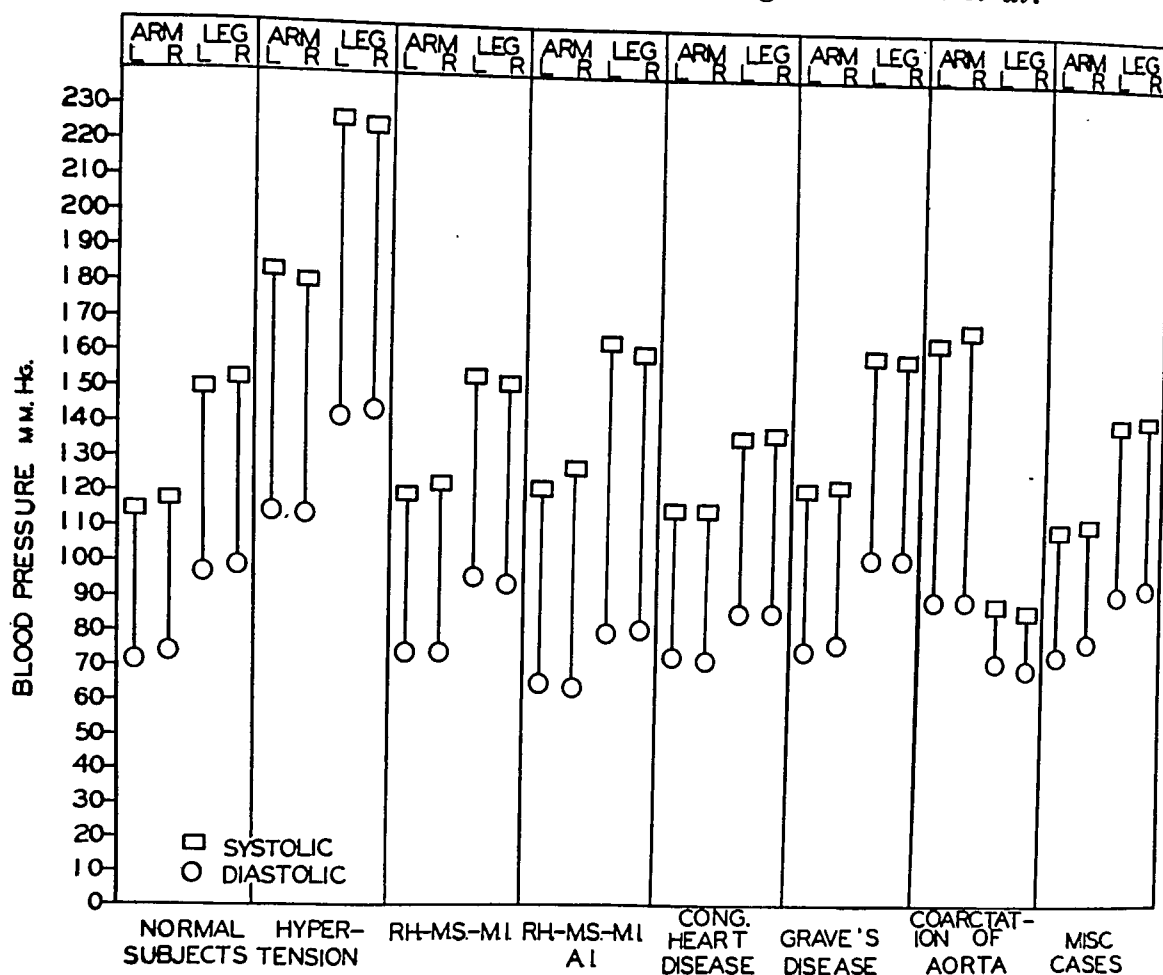


FIG. 9. In this figure the average blood pressures are shown in each extremity for all groups which were studied.

right leg from 100 to 180 mm., averaging 138 mm. Diastolic pressures ranged from 72 to 95 mm. in the left leg, and from 72 to 100 mm. in the right leg, averaging 86 mm. in both lower extremities. Systolic and diastolic blood pressures in the legs were higher than in the arms in all patients with congenital heart disease exclusive of coarctation of the aorta.

Graves's Disease. Observations made on ten patients with Graves's disease are shown in Figure 6. The systolic pressure in the left arm ranged from 108 to 138 mm., averaging 122 mm., and in the right arm from 108 to 140 mm., averaging 123 mm. In the left arm the diastolic pressure ranged from 64 to 90 mm., averaging 75 mm., and in the right arm from 60 to 90 mm., averaging 77 mm. The systolic pressures in the left leg ranged from 136 to 190 mm. with an average of 161 mm., in the right leg from 150 to 166 mm. with an average of 160 mm.

Diastolic pressures ranged from 88 to 130 mm. in the left leg, from 88 to 110 mm. in the right leg, in both lower extremities averaging 102 mm. Systolic and diastolic blood pressures in the lower extremity were higher than in the arm in patients with Graves's disease and these values were higher than in normal subjects.

Coarctation of the Aorta. Data relating to twenty-three patients exhibiting coarctation of the aorta are shown in Figure 7. The systolic blood pressure in the left arm may be seen to range from 120 to 204 mm., averaging 165 mm., the systolic range in the right arm from 128 to 220 mm., averaging 169 mm. The diastolic pressure in the left arm ranged from 60 to 120 mm., averaging 91.5 mm., in the right arm from 60 to 120 mm., averaging 91.7 mm. In the lower left extremity the systolic pressure ranged from 0 (not obtainable) to 130 mm., averaging 88.4 mm., in the right lower extremity

from 0 to 138 mm., averaging 87 mm. Diastolic pressure in both legs ranged from 0 to 110 mm., with an average of 72 mm. in the left leg, and of 70 mm. in the right leg. Thus, in all except Case 9, systolic pressures in the upper extremity exceeded those in the legs.

Miscellaneous Cases. This group was made up of nineteen patients suffering from chronic constrictive pericarditis, suppurative arthritis, gastritis, disseminated lupus erythematosus, diabetes mellitus, sciatica, congenital syphilis, generalized arteriosclerosis, carcinoma of the lung, Hodgkin's disease, bronchiectasis, adrenal tumor, myxedema, beriberi and Raynaud's disease. The blood pressures are recorded in Figure 8 and the diagnoses are recorded in the legend. In the left arm the systolic range was from 90 to 130 mm. averaging 111 mm., and in the right arm 95 to 140 mm., averaging 113 mm. The diastolic range in the left arm was 50 to 90 mm., averaging 74 mm.; in the right arm it was 54 to 90 mm., averaging 78 mm. In the left leg the systolic pressure ranged from 100 to 210 mm., averaging 142 mm.; in the right leg the systolic pressure ranged from 112 to 180 mm., averaging 143 mm. Diastolic pressures in the left leg ranged from 78 to 128 mm., averaging 92 mm. In the right leg they ranged from 74 to 110 mm., averaging 94 mm. It is apparent that in each case both systolic and diastolic blood pressures were higher in the lower extremity than in the arm.

COMMENTS

The blood pressure values which we obtained in the normal group show a close agreement with similar studies of other investigators. Our observations record separately the values in right and left extremity, while data found in most papers in the literature either represent aggregate values or else the specific arm or leg is not indicated. We found the blood pressures in both lower extremities in normal subjects higher

than in the arms, the systolic difference averaging 33.6 mm. and the diastolic 25.1 mm. higher in the legs. As demonstrated previously by Amsterdam and Amsterdam,¹⁹ the average blood pressure was noted to be several millimeters higher in the right extremity.

In fifteen cases of hypertension the same trend was observed. There was a greater difference in systolic pressure between arm and leg however, the systolic leg pressure averaging 43.5 mm. higher than the corresponding arm pressure. The diastolic difference was not as marked, averaging only 29 mm. higher in the legs.

In the cases of rheumatic heart disease with mitral valve lesions only, blood pressure values showed little difference from the normal group. The cases with aortic insufficiency, however, had wider pulse pressures in the upper extremity due in large part to a lower diastolic pressure in the arm. There was also a wider pulse pressure in the lower extremity, and this resulted from an average systolic leg pressure 10 mm. higher and a diastolic leg pressure 15 mm. lower than corresponding pressures in rheumatic cases with only mitral disease.

The blood pressure data in aortic incompetence reported by various observers are not in agreement as to blood pressure differences between upper and lower extremities. Murray³ found a systolic difference of 26 mm. between arm and thigh, but no significant diastolic difference. Williamson⁴ reported that fourteen of twenty-four cases of aortic incompetence showed a higher leg reading. In the remaining cases there was either a higher arm reading or no significant difference. Kotte, Iglauer and McGuire,¹² although observing higher femoral systolic pressures in seven of ten cases with aortic regurgitation, differences greater than in control and hypertensive groups, consider the 13 cm. arm band incapable of giving an accurate measurement of femoral systolic pressure.

The cases of congenital heart disease in our series did not show significant deviation from the normal. The reason why systolic and diastolic pressures in the lower extremities of these cases averaged only 11 to 13 mm. higher than in the arms (as compared to higher values in the normal) is not clear. No data on blood pressure differences in the extremities in congenital heart disease, with the exception of coarctation of the aorta, are found in the literature.

In our cases of Graves's disease, the systolic blood pressures in the upper extremity averaged 5 to 8 mm. higher than in the normal group, and the diastolic average in the arms was about 4 mm. higher than in the normal subjects. The pulse pressure in the upper extremity was not significantly increased. In the legs the average systolic pressure as well as the average diastolic pressure were higher than in the normal group. The systolic blood pressure difference between arm and leg was somewhat increased, averaging 38 mm. in cases of Graves's disease as compared to 33 mm. in normal subjects. The diastolic blood pressure difference between arm and leg averaged 26 mm. Taussig¹³ obtained a systolic blood pressure difference between arm and leg of 37.3 mm. in nine cases of exophthalmic goiter, but the diastolic difference measured only 7.6 mm. The discrepancies may be partly due to the difficulty in accurately recording the diastolic blood pressure.

Our blood pressure findings in twenty-three cases of coarctation of the aorta are similar to those of other observers. Blood pressures in the arm were uniformly higher than in the legs. There was little difference between right and left extremity. Our values are considerably lower than those reported by King¹⁴ in his study of fifty-six cases of coarctation, in which he obtained average systolic values of 189 mm. in the upper extremity and 123 mm. in the leg, and average diastolic values of 92 mm., and 91 mm. in arm and leg, respectively. The dis-

crepancy may arise for several reasons: (1) Averages in King's fifty-six cases were made from a compilation of readings by a large number of observers while ours were made by two observers; (2) our series include many patients in whom sounds were inaudible in the lower extremity, and finally (3) all of our observations were made with the patients in a basal metabolic state.

It is recognized that blood pressures in the legs might also be significantly lowered in cases with marked narrowing or obstruction of the lumen of the vessels to the lower extremities. We did not come upon such patients, however, to use for comparison.

The necessity for taking blood pressure readings in the legs in every patient with systolic pressure over 135 mm., irrespective of age, if cases of coarctation are not to be overlooked is apparent from these observations. The above study serves to demonstrate the reliability, as a diagnostic finding, of the reversal in differential pressures in coarctation of the aorta. Because coarctation of the aorta was not recognized as the cause of hypertension such patients have been referred for splanchnic resection to lower the blood pressure. This is additional reason for measuring the blood pressure in the legs in a patient with elevated pressure. These patients should now be recognized for another reason: Crafoord and Nylin²⁰ and Gross and Hufnagel²¹ have independently devised an operation to overcome the defect in coarctation of the aorta, namely, by resection of the constricted area with end-to-end anastomosis. Because these patients are subject to subacute bacterial endocarditis, rupture, aneurysmal dilatation and heart failure, they should be re-evaluated in the light of these recent advances.

SUMMARY

1. Observations relating to the blood pressures recorded in all four extremities in 123 patients are presented.

2. In the following categories the systolic and diastolic blood pressures were higher in the legs than in the arms: normal subjects, those with hypertension, patients suffering from rheumatic heart disease with mitral stenosis and mitral insufficiency, and those with mitral stenosis and mitral insufficiency together with aortic insufficiency, patients suffering from congenital heart disease, (exclusive of coarctation of the aorta), patients suffering from Graves's disease and a group of patients with a variety of diseases.

3. Higher systolic and diastolic blood pressures were obtained in the arm than in the thigh in twenty-three cases of coarctation of the aorta, a reversal of the situation encountered in normal subjects and in patients suffering from the diseases listed above, indicating the importance of this finding as a diagnostic aid.

4. Patients with rheumatic heart disease with mitral stenosis and insufficiency and also aortic insufficiency show a wider pulse pressure in the lower extremity, due to higher average systolic and lower average diastolic pressures, than rheumatic cases with only mitral valve lesions.

5. Slightly lower average systolic and diastolic values for the lower extremity were obtained in cases of congenital heart disease (exclusive of coarctation of the aorta) than in the normal group.

6. In most groups, including the normal, both systolic and diastolic average pressures tend to be higher in the right extremities.

7. The use of a standard blood pressure cuff for both arm and leg in measuring blood pressure seems justified by its simplicity and convenience, in spite of the possible error introduced by the difference in size of the upper and lower extremities.

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Relative Importance of Certain Variables in the Clinical Determination of Blood Pressure*

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THERE are four variables which have an effect on the indirectly determined blood pressure in the brachial artery of man which have been brought to the attention of the clinician in recent years. They are: the position,²⁻⁵ the venous content,^{3,4} the thickness,⁶ and the location (right or left)⁷ of the arm. The importance of these factors does not seem to have been stressed sufficiently, for there is still a clinical tendency to ascribe significance to changes in blood pressure easily attributable to the error of measurement inherent in the sphygmomanometric method. It is the purpose of this paper to reemphasize these common causes of variance with the method and to add a few observations especially on the relative importance of position and venous content.

POSITION AND VENOUS CONTENT OF ARM

The effect of position and of venous congestion of the arm was determined by a single examiner making measurements with the same sphygmomanometer in the brachial artery of thirty-two young, stable, healthy male subjects. (Table I.) This has been done before in a somewhat different way,^{2,3,4} but it is believed without giving adequate emphasis to the greater effect of position of the arm. The blood pressures were recorded with the subjects recumbent for five minutes and again after standing for

two minutes, observing the details of technic recommended by the American Heart Association.⁸ While recumbent the blood pressure was recorded with the subject's arm at his side. Then he was asked to raise it perpendicular to the bed for twenty seconds. At the end of this time the cuff was re-inflated, the arm brought back to his side, and blood pressure rapidly recorded. In Figure 1 these two determinations are indicated as "before drainage" and "after drainage" to show that they were taken before and after the arm had been drained of venous blood. With the subject standing for two minutes the blood pressure was taken with the arm pendent at the side. It was raised forward and supported at the level of the heart, taken as 5 cm. below the angle of Louis, and pressure recorded again. Each of these determinations was repeated after draining the arm as indicated above.

Results in Figure 1 and in Table I show that although venous drainage does have some effect on the systolic blood pressure with the subject recumbent, and on the diastolic pressure with the subject standing, the position of the arm when the blood pressure is recorded is far more important. Further, with the subject standing with the arm at heart level, venous drainage has little effect, for in this position there is little venous hydrostatic pressure opposing the return flow of blood from the extremity.

* Most of the observations were made at the Army Air Forces School of Aviation Medicine, Randolph Field, Texas.

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TABLE I

Subject	Age	Ht., In- ches	Wt., Lbs.	Blood Pressure, in mm. Hg												Circumference of Arm, in cm.	
				Recumbent 5 min., Arm at Side		Recumbent, Arm at Side		Standing 2 min., Arm Pendent		Standing, Arm at Heart Level		Standing, Arm at Heart Level		Standing, Arm Pendent		10 cm. above Epicon- dyles	10 cm. below Epicon- dyles
B. R. A.	26	69	139	105	71	99	71	115	95	95	67	105	79	109	81	25	26.7
J. A. B.	20	69	147	118	70	126	74	124	84	122	78	124	76	126	84	26.7	25.4
F. L. B.	21	67	138	114	76	108	72	128	100	106	68	102	68	106	90	26.7	26.7
V. P. B.	24	69.5	157	116	74	122	68	128	78	118	70	114	72	120	78	24.7	25.4
M. F. B.	28	65.25	147	120	78	104	64	110	88	100	60	96	62	112	78	28.6	28.6
E. H. B.	27	71	170	122	68	108	60	110	86	98	60	96	56	118	78	27.2	28
G. C.	25	66.75	136	122	72	116	70	118	74	112	68	106	70	110	74	24.1	25.4
M. M. C.	34	71	180	110	78	106	74	126	90	114	78	106	76	118	90	30	30
T. J. F.	23	70.5	176	120	78	118	82	120	100	106	88	120	90	136	94	27.9	26.7
R. R. F.	32	65.25	138	104	52	92	58	110	70	86	60	88	60	110	70	29.2	28
C. R. F.	23	67.5	142	112	78	110	78	106	80	102	76	102	80	108	76	27	26
E. W. G.	20	74.25	173	144	82	138	80	140	100	126	82	124	76	138	108	28	28.6
T. F. H.	21	67	147	118	76	120	70	118	96	114	90	118	84	126	90	26	26
E. J. H.	22	64.5	150	142	88	142	88	152	100	140	90	136	90	150	100	27.3	29.2
H. B. H.	21	71.25	155	128	58	118	58	126	84	104	62	92	58	124	74	27.2	28
R. T. K.	18	64.75	113	140	72	134	76	128	74	130	70	126	68	136	78	24.1	24.7
W. E. L.	18	67.25	115	128	64	118	72	126	92	112	76	108	68	112	90	23.4	24.1
R. L. L.	21	67	182	132	84	126	78	138	90	124	76	114	76	140	94	29.8	29.2
H. S. M.	23	72	185	120	84	108	78	120	94	98	68	94	70	112	86	31	28.6
V. J. M.	20	69	157	146	90	136	86	150	110	134	100	144	88	150	98	29.8	29.8
R. H. P.	32	68	136	116	72	110	78	110	82	100	72	100	64	122	82	26	26
R. C. R.	22	68	149	122	70	120	74	120	100	112	68	106	70	120	90	28	26.7
J. A. R.	33	70	143	108	68	108	74	104	82	96	64	94	74	100	76	26.7	26.7
A. K. R.	27	74.75	158	124	84	132	92	130	98	124	90	128	88	134	100	26.7	27.9
T. H. S.	22	66	140	98	68	102	68	106	78	84	66	96	64	102	74	26.7	26.7
O. E. S.	22	68.75	136	120	80	118	70	130	100	110	70	102	68	130	96	25.4	27.3
R. E. S.	25	69	160	120	76	116	76	114	76	108	76	88	60	112	76	30.5	29.2
E. C. T.	31	71.5	193	124	78	118	80	130	94	112	84	100	84	124	90	29.8	28.6
J. H. T.	21	69.25	139	120	80	110	74	110	90	100	72	96	70	124	88	25.4	26.7
F. P. V.	24	69.5	153	122	80	122	72	126	100	116	78	118	78	144	96	27.9	27.9
P. F. W.	21	67	143	108	66	106	62	106	74	80	64	94	56	96	74	26	25.4
W. J. W.	21	68	166	150	80	146	90	150	90	146	88	138	94	150	90	27.5	28
Mean:	24.0	68.7	152.0	121.7	74.8	117.4	74.0	122.8	89.0	110.3	74.3	108.6	73.0	124.3	85.7	27.2	27.3
Standard Deviation:	4.3	2.5	18.5	12.2	8.1	12.6	8.3	13.0	10.0	15.2	10.2	14.9	10.3	18.4	9.5	1.9	1.5
S. E. of Mean:	.78	.45	3.32	2.19	1.45	2.26	1.50	2.33	1.80	2.73	1.83	2.68	1.86	3.31	1.71	.35	.27

The most obvious reason for the importance of the position of the arm in determining levels of blood pressure would appear to be the hydrostatic column of blood in the brachial artery between the level of the heart and the level of recording blood pressure in the arm. In order to estimate how much effect a column of blood in the brachial artery will have on the blood pressure, the distance from the level of the heart (5 cm. below the angle of Louis) to the antecubital fossa of the pendent arm was measured in twenty subjects and found to average 20.68 cm. In these same twenty subjects the average systolic pressure in the pendent right arm was 115.9 mm. Hg and

the diastolic was 87.3 mm. Hg. By elevating the arm to the level of the heart, these values fell to 105.8 and 74.9 mm. Hg, respectively. The average fall of the two considered together was 11.3 mm. Hg. If this value in mercury is converted to blood, it is equivalent to 14.6 cm. In this series, then, the change in blood pressure was about one-third less than expected on the basis only of hydrostatics. This statement assumes that the Korotkoff sounds are determined by pressure in that part of the vessel over which they are heard. Regardless of cause, the significance of these few observations is that one of the most important variables concerned with

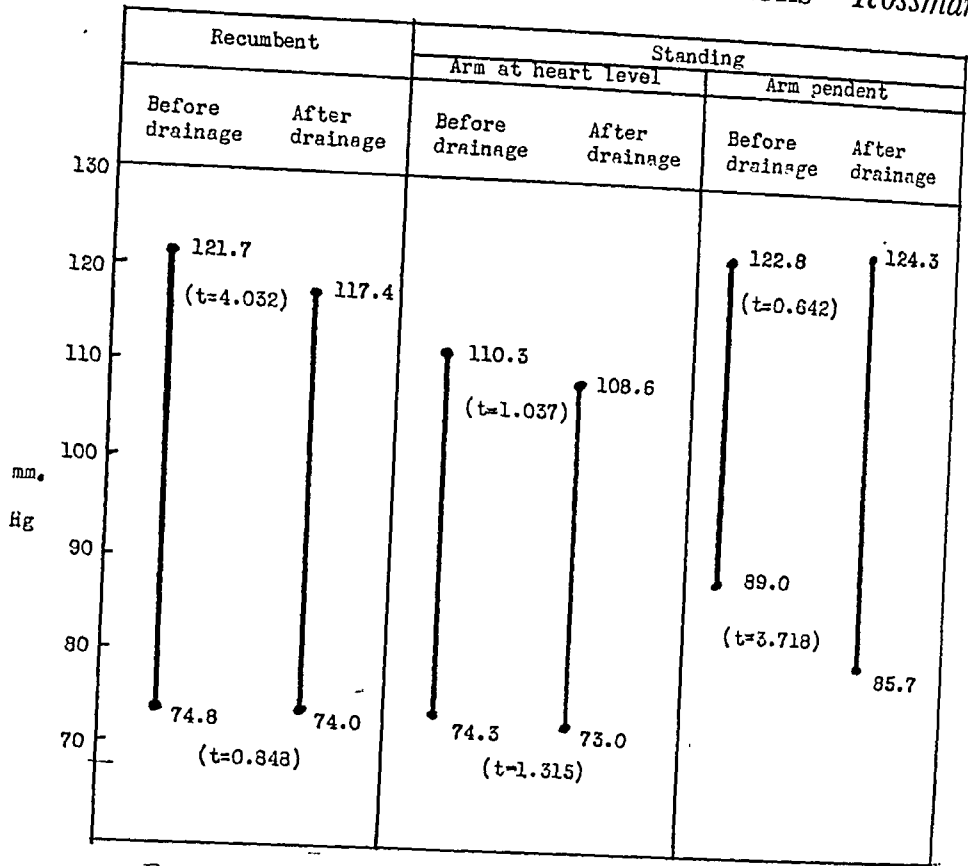


FIG. 1. Mean blood pressures in thirty-two normal subjects.

$$t = \frac{\text{mean difference}}{\text{S. E. of mean differences}}$$

The mean difference is highly significant ($p < 1\%$) if the value of t is greater than 2.75.

the level of blood pressure determined clinically is the position of the arm, and venous congestion is of significance largely as it is caused by this position. As recommended by the American Heart Association,⁸ the arm should always be at the level of the heart (5 cm. below the sternal angle) when recording blood pressures, whatever the posture of the subject may be.

THICKNESS OF THE ARM

On comparing directly determined blood pressure with sphygmomanometric measurements, it has been ascertained that in general the thicker the arm the higher the blood pressure, particularly the systolic pressure.⁶ The importance of this variable was tested further by comparing the thickness of the extended arm 10 cm. above and 10 cm. below the humeral epicondyles with the blood pressure recorded by one observer in

TABLE II
CORRELATIONS OF BLOOD PRESSURE AND CIRCUMFERENCE OF ARM

	Systolic Blood Pressure, Subject Recumbent 5 Minutes		Diastolic Blood Pressure, Subject Recumbent 5 Minutes	
	With Circumference of Arm 10 cm. above Epicondyles	With Circumference of Arm 10 cm. below Epicondyles	With Circumference of Arm 10 cm. above Epicondyles	With Circumference of Arm 10 cm. below Epicondyles
Coefficient of Correlation	.092	.281	.310	.463

the same arm of thirty-two normal subjects in the recumbent position. (Table II.) There was little correlation between the systolic blood pressure and the circumference of the arm at either level. However, there was a fair correlation between the diastolic blood pressure and the circumference of the arm 10 cm. above the epicondyles (coefficient of correlation 0.310), and a good correlation

between the diastolic blood pressure and the circumference of the arm 10 cm. below the epicondyles (coefficient of correlation 0.463). Little can be done to control this particular variable in measuring the blood pressure clinically by the sphygmomanometric method, although clearly the patient with muscular or fat arms is at a disadvantage when rigid criteria of normal blood pressure are utilized.

RIGHT OR LEFT ARM

No experiments were done on the sphygmomanometric measurement of arterial pressure simultaneously in the two arms. However, available data⁷ indicate that the difference in normal subjects is of sufficient size and frequency to make it obligatory to make comparative measurements in the same arm.

SUMMARY AND CONCLUSIONS

1. Blood pressure should always be determined without any part of the arm below the level of the heart (5 cm. below the sternal angle) regardless of the position of the subject.

2. When blood pressure is determined with the arm at heart level the average effect of draining the arm of venous blood is negligible.

3. There is a good positive correlation between thickness of the arm 10 cm. below

the epicondylar line and the level of the diastolic blood pressure. The examinee with thick forearms is at a disadvantage when rigid criteria of normal blood pressure are used.

4. From data available elsewhere, it is obligatory to make all comparative determinations on the same arm.

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Concentration of Renin in Renal Venous Blood in Patients with Chronic Heart Failure*

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THE renal blood flow in patients with congestive heart failure is greatly reduced.^{1,2} It has been shown experimentally that renal ischemia stimulates production of a substance called renin, which causes vasoconstriction.³ It is, therefore, logical to wonder if renin production is increased in patients with cardiac failure. The clinician finds certain phenomena which indicate that active vasoconstriction does occur in heart failure, i.e., the maintenance of normal or increased blood pressure in the presence of a falling cardiac output; the rapid rise in venous pressure in acute heart failure and pericardial tamponade without increase in blood volume;⁴ the early fall in venous pressure without decrease in blood volume and the fall in peripheral resistance which occur when the circulation improves in response to digitalis.⁵ In severe heart failure we have found a reduction in renal blood flow out of proportion to the reduction in cardiac output.² The renal blood flow was reduced to a much greater degree than the filtration rate, suggesting a high filtration pressure. This points to intrinsic renal vasoconstriction, most likely of the efferent arterioles which could be produced by renin.^{6,7} These considerations have led to the investigation of renin production in heart failure.

METHOD

The concentration of renin is determined by a biological assay in which there are many sources of error. Any vasoconstrictor substance formed in the kidney and discharged into the blood stream is greatly diluted by the time blood is collected from the usual site at the elbow. It was obviously desirable to avoid this dilution by obtaining blood directly from the renal vein. This was done by the technic previously described from this laboratory.⁸ A flexible radiopaque catheter was introduced into the venous system through the antecubital vein. Under fluoroscopic control this was threaded through the superior vena cava, right atrium and inferior vena cava into the renal vein. In order to be certain that the catheter was in the renal vein a solution of sodium para amino hippurate* was injected and samples of blood analyzed from the femoral artery and from the catheter. The finding that the hippurate had been extracted as the blood passed through the kidney demonstrated that the catheter was actually in the renal vein. The renin content of blood from the renal vein was compared with that of blood collected simultaneously from the femoral

* Sodium para amino hippurate was obtained through the courtesy of Sharpe and Dohme.

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artery. The use of arterial blood as a control eliminated the presence of vasoconstrictor substances which might have been present from sources other than the kidney or which might have been formed in the blood during the assay. Dogs were used for the assay because they are relatively insensitive to renin and would not be expected to show positive results unless significant amounts were present. Samples of blood from normal subjects and from those with congestive failure were assayed without the observer knowing the source of the samples.

The blood was citrated and iced immediately, then centrifuged as quickly as possible at room temperature. The plasma was separated and frozen with dry ice. It was kept in this state until bioassays could be made conveniently.

The plasma was prepared by the technic of Haynes and Dexter⁹ and the concentrate from 10 cc. of dialysate injected intravenously into dogs anesthetized with sodium pentobarbital (30 mg./K.). Blood pressure rises were recorded graphically through a cannula placed in the carotid artery. Frequent intermediate injections of angiotonin were given, calculated to produce a standard rise of 20 to 35 mm. Hg in the test animals. Since dogs are approximately one-fourth as sensitive to renin as cats, four times as much angiotonin was used in our dogs as is used in cats. The number of dog units was determined from the formula:

$$X = \left(\frac{Y}{St} \right)^2$$

X = number of dog units

Y = rise in blood pressure produced by the unknown

St = rise in blood pressure produced by the standard

RESULTS

Normal Subjects. Renin assays were carried out on renal venous blood and arterial

blood from five normal subjects. No renin was detected in either the renal venous or arterial bloods. Renal venous blood from normal subjects has been found by Dexter¹⁰ and Page, E. W.¹¹ to contain small amounts of renin in about half the cases. Cats used by Dexter are about four times as sensitive to renin as dogs used in our experiments. Page used the rat uterus. It is likely that we should have found small amounts in the renal venous blood if we had used more sensitive animals.

TABLE I
OBSERVATIONS IN ELEVEN PATIENTS IN CHRONIC CONGESTIVE FAILURE

Patient	Renal Plasma Flow Cc. per 1.73 sq. m. per mm.	Filtration Rate Cc. per 1.73 sq. m. per mm.	Filtration Fraction	Units of Renin in Renal Venous Blood	B. P. Rise in Dog Mm. Hg	Arteriovenous O ₂ Difference	
						Systemic	Renal
J. C.	91	37	40.6	.56	24	7.9	4.4
L. H.	177	64	36.2	1.14	28	6.8	4.4
L. F.	248	57	23.0	.49	18	6.3	2.5
L. H.	157	70	44.6	.25	10	6.3	3.8
W. L.	272	93	34.6	.00	0	5.2	2.4
S. H.	174	72	41.0	.36	20	5.0	4.0
J. M.28	16	5.1	2.5
J. McW.	269	84	31.4	.39	24	4.9	2.8
C. McM.	326	131	40.2	.54	22
L. V. E.	264	99	37.5	.00	0	5.9	2.8
M. L. K.	332	96	29.0	.00	0	5.2	2.8

Patients with Congestive Failure. Observations were made on eleven patients with heart failure. The renal blood flow was reduced in all. No renin was found in any of the samples of arterial blood, but it was detected in significant amounts in eight of the eleven patients with heart failure. (Table I.) There was no definite correlation between the amounts found and the renal blood flow, but the technic used is too crude to be considered quantitative.

Why three of the samples of blood from the renal vein did not contain sufficient renin to be detected by the technic used was not determined. It may be that the renal blood actually contained little renin. It is possible that some blood was aspirated from the vena cava or that the tip of the catheter lay near the mouth of a vein entering the renal vein from some other organ than the kidney or that the dog as an experimental animal is too insensitive to respond to smaller concentrations of renin.

COMMENTS

These observations demonstrate that renin is present in a high concentration in the renal blood in the majority of patients with severe congestive failure. This finding further confirms the observations of Merrill² that the renal blood flow in patients with severe congestive failure frequently falls to a level as low as one-fifth of the normal value. Renal venous blood in these patients should afford a potent source of human renin for experimental studies.

From the data reported here it is not possible to compare quantitatively the production of renin in patients with chronic failure with that in normal subjects. The renal blood flow in patients with chronic failure was one-third to one-fifth that present in the normal subjects. If the production of renin by the kidney was the same in both groups of subjects, it would be more concentrated in those with the slow blood flow.

There is considerable evidence that vasoconstriction occurs in heart failure. The cardiac output falls to a greater extent than does the arterial pressure. This finding is indicative of arteriolar constriction. The renal blood flow is greatly reduced and the high filtration fraction suggests that efferent constriction is greater than afferent constriction.⁶

Part of the changes in venous pressure seems to result from vasoconstriction. The rise in venous pressure seen in patients with congestive heart failure seems best explained by two mechanisms, increase in blood volume and increase in vasoconstrictor tone. Warren and Stead show that in patients with fixed chronic heart failure the venous pressure varies with the blood volume.¹² In patients with acute pericardial tamponade, relief of the tamponade causes an immediate fall in venous pressure which is not caused by a change in blood volume.¹³ In patients in whom the administration of digitalis causes the circulation to improve, an early fall in venous pressure occurs which is not the result of a decrease in blood volume.⁵ These changes in venous pressure seem best explained by a redistribution of blood within the vascular bed as a result of changes in tone of the vascular system.

At least three of these manifestations of congestive heart failure, i.e., well maintained peripheral resistance in the presence of a decrease in cardiac output, decreased renal blood flow out of proportion to fall in cardiac output and production of renin, also occur in acute hemorrhage.^{14, 15, 16} They are probably a manifestation of the reduced cardiac output itself. At first glance one is surprised to find such a striking similarity between the dynamics of acute hemorrhage and congestive failure as these conditions present very different clinical pictures. In hemorrhage the venous pressure is low; in heart failure, high. This difference does not necessarily mean that vasoconstriction has not occurred in both conditions. In the patient with hemorrhage, the blood volume has simply fallen so low that vasoconstriction cannot maintain a normal pressure. In heart failure the same degree of vasoconstriction with a normal blood volume will produce an elevated venous pressure. If the heart failure is of some duration and

SUMMARY

the blood volume is increased, an even more striking rise in venous pressure may occur. These relationships between blood volume and venous pressure have been recorded elsewhere.¹³

The edema so characteristic of heart failure is absent in patients with acute hemorrhage, but in both groups of patients oliguria is the rule. The patient with acute hemorrhage either recovers or dies in a relatively short time. If he should survive with an inadequate circulation and oliguria, edema would form if given sufficient salt and water over a long enough time.

The fact that renin is produced by the kidneys in congestive failure and that generalized vasoconstriction occurs does not necessarily mean that the renin produces the vasoconstriction. From the data at hand two explanations are equally possible. Vasoconstriction in the kidney may occur from reflex stimulation when the cardiac output falls. The fall in renal blood flow from reflex vasoconstriction then may stimulate the production of renin which may or may not be responsible for some of the other vasoconstrictor phenomena observed. On the other hand, the fall in blood flow in all organs might be equal when the cardiac output becomes inadequate. The fall in blood flow through the kidney might then stimulate renin production which might cause active vasoconstriction in the kidney and other organs.

These observations on the increased renin concentration of renal venous blood in patients with congestive heart failure offer a new approach to the study of some of the clinical phenomena observed in heart failure. They stimulate our interest in the mechanisms by which the venous pressure becomes high in congestive heart failure and make us conscious of the need for further investigation of the mechanism causing renal vasoconstriction when the cardiac output is inadequate.

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1. Renal venous blood was obtained from five normal subjects and eleven patients with fixed chronic congestive failure. A catheter introduced into the antecubital vein was threaded through the venous system into the renal vein. Dogs were used for the assay of renin.

2. No renin was detected in the renal venous blood or arterial blood of the normal subjects. It is to be noted that the dog is only about one-fourth as sensitive to renin as the cat.

3. Significant amounts of renin were found in the renal venous blood of eight of the eleven patients with chronic heart failure. No renin was detected in the arterial blood.

4. The finding of increased concentration of renin in the renal venous blood of patients with chronic congestive failure is additional evidence in support of the finding that the renal blood flow is greatly reduced in chronic heart failure.

5. The well maintained blood pressure in the presence of a low cardiac output, the sudden changes in venous pressure produced by relieving pericardial tamponade and by improvement of the circulation by digitalis, and the marked fall in renal blood flow out of proportion to the fall in cardiac output all suggest that active vasoconstriction is present in patients with heart failure. No final conclusion can be reached at this time as to whether renin is responsible for some of the observed vasoconstriction.*

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Relief of Pellagrous Glossitis with Synthetic Folic Acid*

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OUR working hypothesis in the study of nutritive failure during the past fifteen years may be stated briefly as follows: Impoverished cells have many disturbances operating in their biochemical systems simultaneously. If the nutrients necessary to correct these disturbances are not supplied, the derangement becomes more and more widespread. Each specific corrective measure applied would tend to lead toward normal. Almost full nutritive restoration, however, can come only after long continued administration of all the needed essential substances. In studying pellagra and associated deficiencies, we have placed particular emphasis on the interrelationship between the clinical manifestations of the various syndromes. A certain relative degree of specificity has been studied by ourselves and by others. Frequently, we have seen the administration of a nutrient specific for a single deficiency not only correct that deficiency but cause considerable general improvement in the patient.

Early in my studies on the interrelationship between pellagra and certain macrocytic anemias frequently found in pellagrins, I found that very large doses of ventriculin, liver or liver extract were beneficial in relieving the pellagrin but that the small amounts of liver extract which will produce a remission in Addisonian pernicious anemia in relapse were insufficient to re-

lieve the signs and symptoms of severe pellagra. Later I noted that niacin, which is effective in relieving pellagrous glossitis, dermatitis and the gastrointestinal disturbances of pellagra, did not correct the associated macrocytic anemias. For a number of years I have thought that vitamins and enzymes should work through certain biochemical systems in the body and that a considerable number of chemical substances might affect these biochemical systems in such a way as to produce a satisfactory therapeutic result. The present communication is concerned with the remission of macrocytic anemia and of pellagrous glossitis in two persons following the administration of synthetic folic acid.

CASE REPORTS

CASE I. J. S., a sixty-three-year-old white man, had been under observation in the Nutrition Clinic from 1939 to 1946. When he was first seen, a diagnosis of nutritional macrocytic anemia and pellagra was made. His initial red blood cell count was one million and his initial hemoglobin content was 32 per cent. He had free hydrochloric acid, pepsinogen and rennin in the gastric contents after histamine stimulation. The bone marrow showed typical megaloblastic arrest. He had extensive pellagrous dermatitis on the dorsum of the hands, on the dorsum of the wrists and on the lower part of the forearms. His tongue showed isolated, clear-cut and well demarcated areas of pellagrous glossitis. His dietary history revealed that for many years he

* From the Department of Internal Medicine, University of Cincinnati School of Medicine; University of Cincinnati Studies in Nutrition at the Hillman Hospital, Birmingham, Alabama. The expenses of this study were borne by grants from Lederle Laboratories, Inc. and Ingalls Foundation.

had existed on an inadequate diet and that he did not eat lean meats. After all baseline determinations were made, he was given daily injections of liver extract, and on the fifth day he experienced a great increase in strength and a feeling of well being. Three days later the reticulocytes peaked at 30 per cent. This response was followed by an increase in red blood cells and hemoglobin. After the former had reached a count of three million, he was allowed to go home with the understanding that he would return. At the time of his discharge, the pellagrous glossitis and dermatitis were essentially unchanged. He felt so much better that he did not wish any more treatment of any kind.

He was visited frequently in his home for observation. Five months after he was discharged, the pellagrous dermatitis and glossitis became much more severe, and his anemia had relapsed and he came to the hospital. He was given a single oral dose of 300 mg. of niacinamide, and within twenty-four hours his tongue was objectively and subjectively normal. Two days later the erythematous border of the pellagrous dermatitis began to fade. His blood values remained unchanged. Daily injections of liver extract were followed by prompt blood regeneration. During the next four years he had several relapses of pellagra and of the anemia. On his last admission in 1945 he was given intramuscularly 0.5 cc. of reticulogen for ten days. He had a prompt and characteristic remission of his anemia, but there was no apparent change in the pellagrous dermatitis or glossitis which was again present on this admission. With all the treatments he had had to relieve his pellagrous glossitis and dermatitis (300 to 500 mg. nicotinic acid daily on four other occasions), in no instance did detectable blood regeneration follow the administration of nicotinic acid.

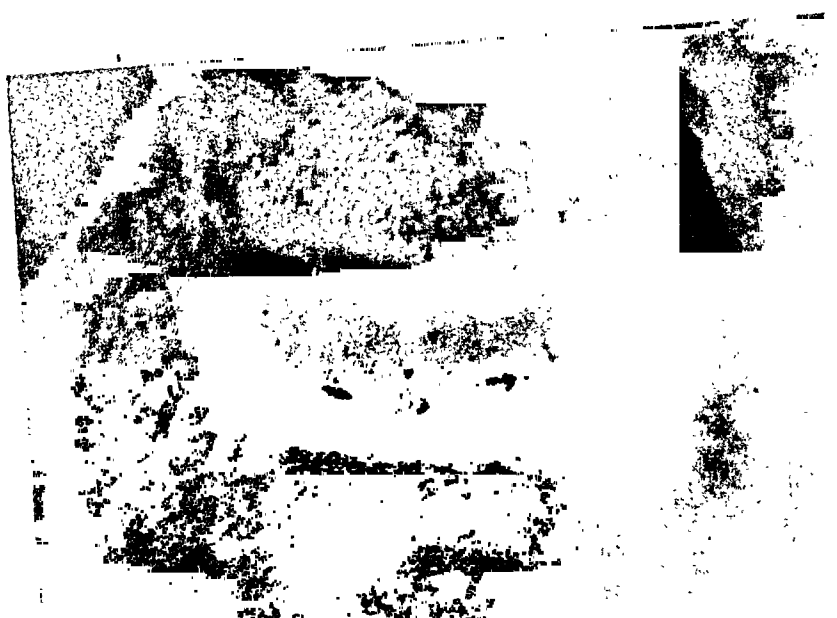
In the spring of 1946 he again had a remission of the anemia and a recurrence of the pellagrous glossitis. (Fig. 1.) This time he was given a daily oral dose of 10 mg. synthetic *Lactobacillus casei* factor after all baseline determinations had been made. Two days later the burning of the tongue disappeared and it appeared less red. By the fifth day there was evidence of a great degree of

healing of the tongue. (Fig. 3.) The reticulocytes peaked at 19 per cent on the seventh day and an increase in red blood cells followed in the usual way.¹

CASE II. B. B., a fifty-five-year-old Negro woman, was admitted to the Nutrition Clinic in 1942 with a diagnosis of Addisonian pernicious anemia and pellagra. Her red blood cell count was 1.7 million and her hemoglobin was 49 per cent. She had no free hydrochloric acid, pepsinogen or rennin in the gastric contents after histamine injection. The bone marrow showed megaloblastic arrest. She had four areas of pellagrous glossitis characterized by being well demarcated, very red and very sore. Areas of pellagrous dermatitis covered both elbows. Her dietary history showed that for the past ten years she had been eating carbohydrates preponderantly. The administration of 0.5 cc. of reticulogen intramuscularly each day for ten days was followed by a characteristic remission of the anemia, but there was no apparent change in the pellagrous glossitis or the dermatitis. She was discharged with her red blood cell level at three million, but she did not wish to report back for additional therapy. She was seen frequently in her home.

Since the pellagrous glossitis persisted, she was given 500 mg. of niacinamide by mouth each day for four days and it healed completely. The red blood count and hemoglobin, which were beginning to fall, were not affected by the administration of niacinamide. During the next four years she had three relapses of pellagra and two of anemia. Each time liver extract relieved the anemia and the niacinamide relieved the pellagrous glossitis. In February, 1946, she had a relapse of the anemia and a recurrence of the pellagrous glossitis. She was admitted to the hospital, baseline determinations were made, and 10 mg. of synthetic *Lactobacillus casei* factor was administered daily by mouth. On the second day she volunteered that her tongue no longer burned. On the fifth day it was subjectively and objectively normal. By this time reticulocyte regeneration had begun. It reached a peak of 16.6 per cent on the seventh day and was followed by a prompt increase in red blood cells and hemoglobin.

1. Photograph of recurrent pellagrous glossitis in Case 1. Note the swollen tongue and erythema in isolated areas of tongue.



2. Photograph of same patient on the fourth day after patient had received 10 mg. folic acid daily. The tongue is less swollen and the areas of pellagrous glossitis are less red.

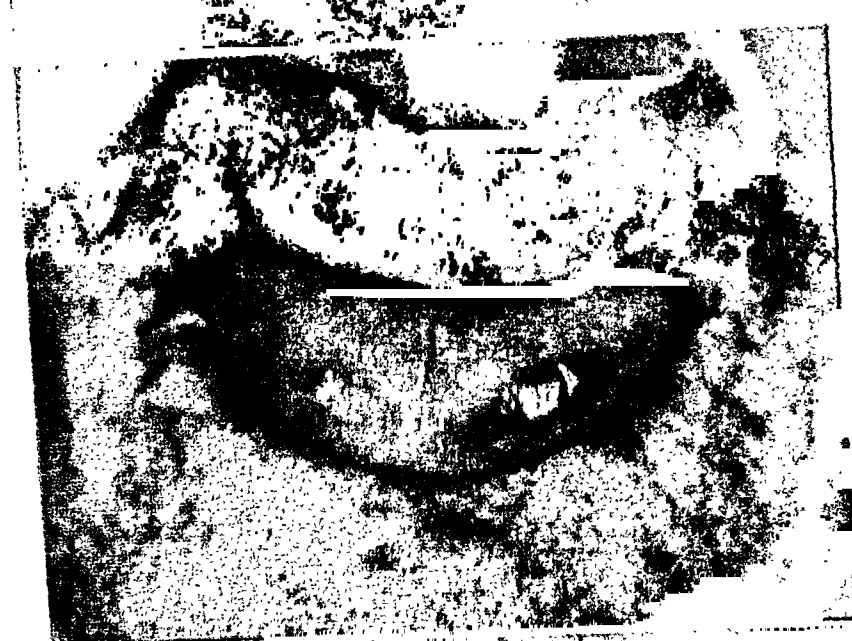
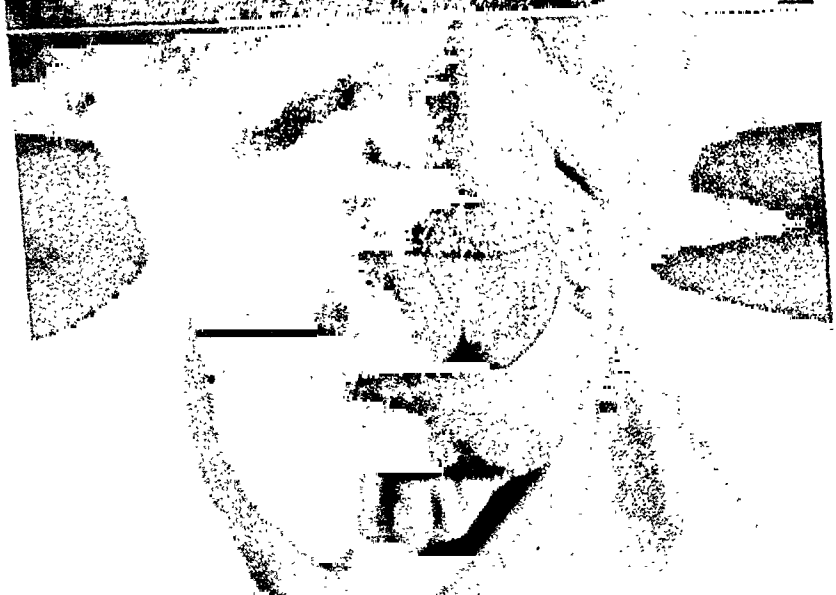


FIG. 3. Photograph of same patient on the fifth day of therapy. The tongue is grayish and the pellagrous glossitis has almost disappeared. One small area of residual change which is still evident disappeared the next day.



SUMMARY AND CONCLUSIONS

Following the administration of synthetic folic acid to two patients with macrocytic anemia in relapse and pellagrous glossitis, there was prompt regeneration of the blood and profound improvement in the glossitis. In both cases several relapses of the anemia had responded to liver extract and the pellagrous glossitis had disappeared following the administration of niacinamide. On no occasion, however, did the glossitis respond to the small doses of liver extract employed nor did any hemopoietic response occur following niacinamide therapy. We previously had observed that great improvement of the entire alimentary tract occurred in persons with sprue following the administration of folic acid and that persons with pernicious anemia and nutritional macrocytic anemia likewise had subjective and objective improvement of their glossitis. Up until the present time, however, synthetic folic acid is the only single chemical substance we have found that is effective in treating both macrocytic anemia and pellagrous glossitis in these two patients.

These observations will result in some unavoidable confusion since clinical medicine has not grown up as an exact science.

Such clinical syndromes will not be entirely explained until we understand human nutrition and nutritional deficiency diseases with all that this implies about the interrelationship of the various nutrients and the overlapping of some of their functions. The clinical improvement described in these patients following a short course of therapy is temporary; and from a practical, therapeutic point of view I recommend that the physician treating similar cases give suitable antianemic therapy and administer a mixture of indicated vitamins and a diet high in proteins for as long as necessary. The author considers niacinamide, not folic acid, as a specific therapeutic agent for the pellagrin. Yet it is well for the physician to realize that each nutrient may well have some specificity and also have a profound and general function in our bodies. Our observations in the two cases reported give support to our working hypothesis that in persons with mixed deficiency diseases there are definite alterations in the biochemical systems which can be corrected by proper therapy.

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Results from Subtotal Gastric Resection in Peptic Ulcer*

The Internist's Viewpoint

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VARIOUS procedures are now available for the management of the patient with a benign peptic ulcer who does not readily recover and remain well on an ordinary dietary and hygienic regimen. Irrespective of the reason for the persistence of the lesion, whether it be a constitutional gastric hyperacidity, some psychogenic factor, an inability or failure on the part of the patient to observe directions or the development of one of the recognized ulcer complications, some additional therapeutic measure is then indicated. This may be a prolonged period of hospitalization with twenty-four-hour neutralization of the gastric acidity, radiotherapy, hormone therapy, the administration of amino acids or some operative undertaking. Obviously, for the patient with an irreversible pyloric obstruction, or, in the instance of a gastric lesion with some doubt as to the benignancy of the ulcer, surgery alone need be considered. In these situations, however, as well as in all the other complications, with the possible exception of perforation, the internist or gastro-enterologist is usually called upon to make the decision regarding the type of therapy that will give the patient his best chance of permanent and satisfactory cure.

In an attempt to clarify the indications for surgical interference and especially to show, for subsequent comparison with other procedures, the probable results from sub-

total gastrectomy, we present in this publication a report on our experience with that operation over an eight-year period. The series does not represent the total experience of our surgeons, or our own total experience, with gastric resection. It includes only the cases that have been studied preoperatively and postoperatively by the senior author in his private office and in the out-patient gastrointestinal section and the wards of the medical clinic of this hospital; also, only those that we have been able to follow to date. It does, however, include, in addition to the so-called refractory cases, all those patients who were operated upon for repeated hemorrhage, for pyloric stenosis and for roentgen evidence of deep penetration or perforation of the gastric, duodenal or jejunal wall, but none that subsequently was proved to be malignant.

SUBJECTS AND DATA

The data are from 113 cases, all operated upon from October, 1938, through 1945; only three, otherwise acceptable, have been eliminated because they could not be followed either by personal interview or correspondence. Earlier cases have not been included, because before 1938 extensive gastric resection was not frequently employed for peptic ulcer in this hospital. Since then a subtotal gastrectomy with an antecolic Balfour or Hofmeister end-to-side gastro-

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jejunostomy has been the usual operative procedure.

Obviously, many of the cases have been followed for only one or a few years, but it will be noted below that up to, and even beyond, five years the results of the follow-up period for each year were approximately the same.

As cured we have included only those patients with no residual digestive symptoms; as improved, those that have been relieved of their previous symptoms of ulcer type, but still have vague digestive symptoms of the sort often encountered in patients without demonstrable organic disease of the digestive tract; and as unimproved, those that have continued to present symptoms or roentgenological evidence of ulcer or of one of its complications. These latter must be regarded as surgical failures, and to them special attention will be directed. We have also listed in our tables, for their effect on the statistical results, those that have died, either from the operation itself or subsequently from some complication.

TABLE I
AGE AND SEX IN 113 PATIENTS WITH PEPTIC ULCER
SUBJECTED TO GASTRIC RESECTION

Age in Decades	Male	Female	Total
20-29	6	3	9
30-39	12	6	18
40-49	18	6	24
50-59	35	8	43
60-69	14	2	16
70-79	3	0	3
Totals	88	25	113

Table I shows the sex and age of the 113 patients at the time of operation. Eighty-eight, or 78 per cent of them, were of the male sex and the largest number, 43, or 38 per cent, were in the sixth decade of life. More than a half of the total number, 59 per cent, were in the fifth and sixth decades. It is particularly interesting that three were

in the eighth decade; one of these was seventy-nine years old and today is active and well at eighty-two.

Table II indicates that in twenty-four of the cases the ulcerative lesion was gastric in location; in seventy-three duodenal; in ten both gastric and duodenal, and in six gastro-jejunal or marginal (secondary to previous gastro-enterostomy). It also shows that of the total, forty-two were resected because of the refractory nature of the ulcer (not satisfactorily responsive to the medical regimen); twenty-three because of recurrent hemorrhage, and nineteen because of pyloric stenosis; while in sixteen a malignant lesion could not otherwise be eliminated with certainty, and in thirteen deep penetration of the wall either had been demonstrated by roentgen ray studies or was suspected clinically. In two of the latter cases subacute perforation had occurred.

TABLE II
INDICATION FOR GASTRIC RESECTION IN 113 PATIENTS
WITH PEPTIC ULCER

Indication for Operation	Location of Lesion				
	Gastric	Duodenal	Gastric and Duodenal	Marginal	Total
Refractory to medical therapy	5	33	2	2	42
Recurrent hemorrhage....	3	15	2	3	23
Stenosis.....	3	13	2	1	19
Possible malignant degeneration...	10	3	3	0	16
Deep penetration.	3	9	1	0	13
Totals.....	24	73	10	6	113

Table III shows the results obtained from the resection for each location of the ulcer. More of the gastric ulcers were completely cured (95.8 per cent) than of any other type, and all of them were either cured or improved. Of the duodenal ulcers 79.4 per cent were cured and 13.7 per cent im-

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TABLE III
RESULTS FROM SUBTOTAL GASTRIC RESECTION IN 113 PATIENTS WITH PEPTIC ULCER PERFORMED FROM 1938 TO 1945

Present Condition	Number of Cases by Location of Lesion					
	Gastric (Per Cent)	Duodenal (Per Cent)	Gastric and Duod. (Per Cent)	Marginal (Per Cent)	Total (Per Cent)	Total of Primary Resections (Per Cent)
Cured.....	23 (95.8)	58 (79.4)	7 (70.)	2 (33.3)	90 (79.6)	88 (82.3)
Improved.....	1 (4.2)	10 (13.7)	0 (0)	0 (0)	11 (9.7)	11 (10.3)
Unimproved.....	0 (0)	3 (4.1)	3 (30.)	3 (50.)	9 (8.0)	6 (5.6)
Died, postoperatively.....	0 (0)	1 (1.4)	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Died, subsequently.....	0 (0)	1 (1.4)	0 (0)	1 (16.6)	2 (1.8)	1 (0.9)
Total number.....	24 (100)	73 (100)	10 (100)	6 (100)	113 (100)	107 (100)

proved, a total of 93.1 per cent. When both a gastric and a duodenal ulcer were present the result was less favorable, 70 per cent cured, and for the ulcer that developed in the stomal area after a previous gastroenterostomy, it was largely unfavorable (only one-third cured). If the latter cases are excluded, the results for primary operation are found (last column) and they indicate complete cure in 82.3 per cent with improvement in an extra 10.3 per cent, a favorable result in 92.6 per cent.

In order to test the reliability of our data on the more recently operated cases, Table IV shows a break-down of the results in the total 110 surviving patients for the period of their follow-up. It will be noted that for the first, second and third years after resection the percentage of those cured and of those improved, taken together, is approximately the same (91.8, 90 and 89.6). For those operated four and for those five or more years previously the combined cured and improved percentage was only slightly less favorable (87.9 and 87.5). Thus it is obvious on the basis of our data, that an

almost equally favorable result from gastric resection may be expected after five years, there occurring only a slight decrease with each succeeding year.

TABLE IV
RESULTS FROM GASTRIC RESECTION IN 110 SURVIVING PATIENTS WITH PEPTIC ULCER ACCORDING TO TIME AFTER OPERATION (1938-1945 INCLUSIVE)

Time after Operation	Total Number	Physical Status		
		Cured	Improved	Unimproved
Under 1 year.....	110	90 (81.8)	11 (10.1)	9 (8.2)
2 years.....	70	58 (82.9)	5 (7.1)	7 (10.0)
3 years.....	47	39 (81.3)	4 (8.3)	5 (10.4)
4 years.....	33	26 (78.8)	3 (9.1)	4 (12.1)
5 or more years...	16	12 (75.)	2 (12.5)	2 (12.5)

The unimproved patients, including those who died, are covered more specifically in Table V. This shows that of the three patients who died, one (F. W.) succumbed on

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TABLE V

SPECIAL DATA ON TWELVE PATIENTS WHO WERE UNIMPROVED, INCLUDING THREE WHO DIED

Initials	Sex/ Age	Location of Ulcer	Reason for Operation	Amount of Stomach Removed	Ulcer and Pylorus Removed	Previous Surgery	Post- opera- tive Acid- ity, Free/ Total	Subsequent Developments	Possible Explanation for Unfavorable Results
F. W.	M/50	D.	Hem.	$\frac{2}{3}$	Yes	None	Death on 4th p.o. day with peritonitis secondary to subphrenic abscess.	Diabetes. Preoperative perforation.
A. P.	M/62	D.	Sten. Refr.	$\frac{1}{3}$	No	None	0/32*	Duodenal stump perforated 13th day. Died of hem. 12th mo. X-ray negative.	Inadequate resection. Ulcer not removed.
J. S.	M/57	M.	Hem.	$\frac{1}{3}$	Yes	13 yrs.: gastroenterostomy.	18/26	Jejunal ulcer perforated at 6 mos. Then repeated hemorrhages. Died 27 months.	Inadequate resection with secondary operation. Continued acid secretion.
Q. M.	M/48	D.	Hem.	$\frac{1}{3}$	No	None	Jejunal ulcer perforated after 4 months.	Inadequate resection. Ulcer and pylorus not removed.
N. S.	M/27	D.	Refr.	$\frac{2}{3}$	No	6 yrs.; perforation oversewn.	0/14*	Vomiting, nervousness and weakness, but no pain for 6 yrs. X-ray negative for dumping.	Secondary operation; ulcer and pylorus not removed. Functional intestinal disturbance. Uncooperative.
A. D.	M/27	D.	Refr.	$\frac{1}{2}$	No	None	5/15*	Hemorrhaged 7th and 13th p.o. days. Recurrent symptoms after 3 years.	Allergic. Inadequate resection. Ulcer and pylorus not removed.
D. S.	M/33	G, D.	Hem. Refr.	$\frac{1}{3}$	Yes	None	30/50	Jejunal ulcer in 6 mos. Additional resection in 22 mos., but ulceration and free acid persist.	Associated gastritis and alcoholic. Inadequate resection and continued acid secretion.
B. L.	F/61	G, D.	Hem.	$\frac{1}{2}$	G=yes D=no	None	Recurrent hemorrhages after 1 year. X-ray negative for stomal ulcer.	Inadequate resection. Duodenal ulcer not removed. Psychoneurotic.
T. C.	M/26	G, D.	Hem. Refr.	$\frac{3}{5}$	No	None	30/40	Jejunal ulcer after 2 years.	Alcoholic and uncooperative. Inadequate psychopath. Ulcer and pylorus not removed. Continued acid secretion.
A. K.	M/59	M.	Hem. Refr.	$\frac{2}{3}$	Yes	23 years; pylor-ectomy and gastro-enterostomy.	Repeated hemorrhages.	Associated hemorrhagic gastritis. Secondary operation.

TABLE V.—(Continued)

Ini- tials	Sex/ Age	Loca- tion of Ulcer	Rea- son for Oper- ation	Amount of Stom- ach Removed	Ulcer and Pylorus Removed	Previous Surgery	Post- opera- tive Acid- ity, Free/ Total	Subsequent Developments	Possible Explanation for Unfavorable Results
W. R.	M/30	M.	Refr.	$\frac{2}{3}$	Yes	18 mos.; pylorec- tomy and gastro- enterostomy, 4 mos.; excision of stomal ulcer.	0/32*	65 lbs. wt. loss, weakness and par- tial intermittent internal obstruc- tion.	Secondary opera- tion. Total of seven abdominal operations.
L. K.	M/59	M.	Hem.	$\frac{2}{3}$	Yes	7 years; gastroen- terostomy.	40/52	Recurrent jejunal ulcer.	Secondary opera- tion. Psychoneu- rotic. Continued acid secretion.

* After histamine.

the fourth postoperative day and the death due to peritonitis secondary to a subdiaphragmatic abscess which had resulted from perforation prior to resection. The second death occurred in a patient (A. P.) whose duodenal stump perforated at the end of the second week and who required for that a second operation. He then recovered, but a year later died as a result of repeated hemorrhage. The final death occurred in a patient (J. S.) who had had a gastroenterostomy in 1924, was resected in 1938 and then developed a marginal ulcer that required further resection in 1939; he again developed an ulcer with recurrent hemorrhage and died in the twenty-seventh month after his original resection.

Analysis of the data in Table v for the total group of twelve cases, in which the results were unfavorable, reveals: (1) that six had one-half or less of the stomach removed, and, with some overlapping, that six of them did not have the ulcer itself removed (a total of eight in one or the other or both categories); (2) that of the remaining four cases, three (A. K., W. R. and L. K.), as well as two of the above eight, had had previous surgery on the stomach

and the other patient (F. W.) had a subphrenic abscess at the time of the resection; and (3) that four of the total group were psychoneurotic (one a confirmed psychopath), that two of these were alcoholic and that a fifth patient was highly uncooperative in the subsequent management of his case.

Postoperative gastric analyses were not done routinely in the series but of the unimproved patients it will be noted that two had a free acidity of 30 units and one of 40 units (the latter one having had two thirds of the stomach removed).

The failure to regain weight after a gastric resection has been noted by various authors, and so in Table vi are presented certain data on this subject in 100 of our cases. More than half of them (52 per cent) were five or more pounds under their usual weight at the time of the last follow-up examination, and their average weight loss was 19.6 pounds. Only 13 per cent had gained more than five pounds, while 35 per cent remained at about the same weight. Weight loss was most frequently encountered in the duodenal and marginal ulcer cases (56.1 and 60 per cent, respectively).

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TABLE VI
WEIGHT CHANGES GREATER THAN 5 POUNDS IN 100 PATIENTS WITH PEPTIC ULCER FOLLOWING
GASTRIC RESECTION (1938–1945)

Type of Ulcer	Gained		Lost		Unchanged	Total of Each type
	Number, Per Cent	Average gain in lbs.	Number, Per Cent	Average loss in lbs.	Number, Per Cent	
Gastric.....	5 (23.8)	10.8	9 (42.9)	16.6	7 (33.3)	21 (100.)
Duodenal.....	4 (6)	11.5	37 (56.1)	18.5	25 (37.9)	66 (100.)
Gastroduodenal.....	3 (37.5)	13.0	3 (37.5)	24.3	2 (25.0)	8 (100.)
Marginal.....	1 (20.0)	10.0	3 (60.0)	38.0	1 (10.0)	5 (100.)
Totals.....	13		52		35	100
Wt. change average, in lbs.....		11.5		19.6		

COMMENTS

The data obtained in this series of peptic ulcer cases subjected to subtotal gastric resection are at variance with some of those reported in the surgical literature for the past six years. Mage,¹ in a report on 600 patients who survived the operation at the Mt. Sinai Hospital in New York City between 1923 and 1940, found recurrent ulceration in forty-one, ulcer symptoms without convincing evidence of such recurrence in ten, and some disturbance of gastric function, presumably due to the operation itself, in an additional sixty. Thus, excluding his operative mortality, he had unsatisfactory results in 18 per cent. Heuer,² in a careful analysis of his personal experience with 139 patients followed from one to ten years, had unsatisfactory results in 15.1 per cent; this, however, including his operative mortality of 7 per cent. In a review of the literature he found that nineteen authors, together covering 1,196 cases only 67 per cent of which were followed, had a similar result for a shorter period, one to five years, while twenty-two authors, for a one to twenty-year period, admitted failure in 17.3 per

cent. In his own series of cases followed from five to ten years, only two-thirds were entirely relieved of symptoms. Walters, Lewis and Lemon,³ reporting on 197 patients with duodenal ulcer operated upon and followed at the Mayo Clinic from 1929 to 1939, found that only 2.5 per cent developed a recurrent anastomotic ulcer, though an additional 14 per cent had subsequent gastric symptoms. Rienhof,⁴ on the other hand, has reported 90 per cent eventually cured or improved in a series of 260 duodenal cases, though twenty-six of these patients required reoperation; Miller⁵ reported 90 per cent cured and the remaining 10 per cent improved in a series of 173 patients who survived the operation (mortality, 2.8 per cent). Wangenstein⁶ has reported a very remarkable result in 300 consecutive gastric, duodenal and gastrojejunal patients, having had no ulcer recurrence. He does not, however, give the number that had subsequent digestive symptoms. Kiefer,⁷ of the Lahey Clinic, reported on 222 survivors of resection, having had no ulcer recurrence in forty-nine gastric cases, but apparently 9.6 per cent in 146 duodenal cases and 22.2 per cent in 27 marginal cases. Allen and

Welch,⁸ also of Boston, had but two recurrences in forty-three survivors from resection for duodenal ulcer before 1938, and no recurrences in seventy-one survivors of 76 patients operated upon after that time.

The postoperative mortality has varied considerably. Heuer's² review of the literature showed an average mortality of 6.8 per cent, and his own was slightly higher. He admits, however, that the rate has been steadily declining. Lahey and Marshall⁹ found theirs to be 2.7 per cent, exclusive of those with a gastrojejuno-colic fistulous tract; 3.2, when the fistulous tracts were included, and 4.4 for gastrojejunal ulcer alone. Only 2 per cent of Rienhof's patients died post-operatively. These figures may be compared with ours of 0.9 per cent.

The literature reveals that the results have *not* been particularly favorable in the patients who had had previous gastric surgery (secondary resection). Holman and Chenowith,¹⁰ in twenty-six such cases, got a good result in only nineteen (73 per cent). Sanders¹¹ had a mortality of 3.6 per cent in twenty-eight previously operated patients as against 2.7 for his seventy-three primary resections. In our series it has been shown that of the twelve unimproved patients, five had had previous gastric surgery, and that of the six resected for a marginal ulcer, only two are recorded as cured. This may be contrasted with cure or definite improvement in 92.6 per cent of our patients undergoing a primary resection.

Another unfavorable factor in the results from gastric resection would seem to be the failure on the part of the surgeon to remove the ulcer itself and an adequate portion of the stomach. Kiefer⁷ reported seven recurrent ulcers and three postoperative hemorrhages in thirty patients in whom the pylorus and duodenum were not included in the resection. Even when the portion of the duodenum that includes the ulcerative lesion cannot be removed Allen and Welch⁸

have insisted that the mucosa of the antrum and duodenal cap should be excised. Furthermore, it is now the generally accepted opinion among surgeons that in all instances, one-half to two-thirds of the stomach should be excised. Wangenstein insists on a removal of three-fourths of the stomach and always of the antral mucosa. In six of our twelve patients who did badly after operation the ulcer had not been removed, and in four of these six, and in two others, one-half or less of the stomach had been resected.

The final unfavorable factor, and one that especially interests the gastroenterologist, has to do with the emotional state of the patient, his personal habits and his ability and willingness to cooperate. As already stated, four of our unimproved patients were clearly psychoneurotic, two of them also being alcoholic, and one other patient failed entirely to cooperate in his subsequent management.

These observations consequently suggest that the poor results from subtotal gastric resection may be blamed, in part, on an inadequate operative procedure and, in part, on an inadequate personality of the patient. This is not intended to imply that the surgeon should in every case remove the ulcer-bearing area and more than half of the stomach or that the internist should refuse to sanction surgical interference in the psychoneurotic patient. In many instances, as we believe was true for most of our series of unimproved patients, the ideal operative procedure may be technically inadvisable and no other form of therapy may be regarded as justifiable. At the same time these observations indicate the conditions under which a somewhat guarded prognosis must be entertained. Furthermore, when such conditions can be eliminated in the individual patient, one is enabled to present a more hopeful outlook.

Ingelfinger,¹² in a review of the physio-

logical disturbances of the patient who has had a gastrectomy, emphasizes the frequency of reduced weight and calls attention to the confirmatory observations of Church and Hinton,¹³ of Browne and McHardy,¹⁴ and of Miller.⁵ He details, however, certain evidence to indicate that eventually the tendency to remain underweight is less marked. In an attempt to explain the early weight loss, Ingelfinger discusses the "dumping syndrome," due to overfilling of the jejunum from quick emptying of the stomach, with a consequent feeling of fullness, nausea, weakness and giddiness. In spite of his estimate of a 10 per cent incidence of postgastrectomy indigestion, however, only two of our patients have had, even transiently, phenomena suggestive of the "dumping syndrome" or any other digestive disturbance. In fact, in most instances the appetite has been good and the intake of food equal to or in excess of that previously consumed. Ingelfinger also refers to defects in absorption from the intestine after gastrectomy, and more recently, Wollaeger, Comfort, Weir and Osterberg,¹⁵ of the Mayo Clinic, have demonstrated conclusively a deficiency of fat absorption after gastric resection, which is the most probable explanation for the difficulty in gaining weight. In a series of carefully studied subjects they found the amount and percentage of total lipids in the stools of the gastrectomized cases to average more than twice that of controls, the increase being most marked in those with postcibal distress. Among the possible factors for this loss of fats and calories in the feces, they mention rapid emptying of the stomach, intestinal hurry and a diminished flow of pancreatic and biliary secretions.

The significance of allergy in relation to the after-effects of subtotal gastrectomy is uncertain. One of our patients who was allergic to certain food substances did poorly, bled on the seventh and thirteenth

postoperative days and after three years had a recurrence of symptoms, but he also had an inadequate resection and the duodenal ulcer was not removed. Another highly allergic patient since his resection has had no difficulty in eating all of the foods that previously caused severe gastrointestinal upsets. In this patient, as in many others, there has been no impairment of appetite, his intake of food has been much greater than before operation, his physical and mental activities have not been impaired, and yet his weight is persistently about 20 pounds below his previous average.

CONCLUSIONS

An analysis of the results in 113 cases of peptic ulcer subjected to partial gastric resection over an eight-year period leads to the following conclusions:

1. The unfavorable factors in the clinical results are: (1) Lack of cooperation on the part of the patient, (2) failure on the part of the surgeon to remove the ulcer, or at least the pyloric mucosa, and one-half or more of the stomach, and (3) previous gastric surgery.
2. When these factors are eliminated and the surgical technic is good, a favorable result may be anticipated in 95 per cent or more of the cases.
3. In the series of cases herein presented primary resection led to cure or marked improvement in 100 per cent of the patients with gastric ulcer and in 92.6 per cent of the patients with duodenal ulcer.

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The Nisulfazole Treatment of Chronic Ulcerative Colitis*

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FOLLOWING the discovery that sulfanilamide had marked therapeutic value, many investigators became interested in the possible value of various derivatives. We became interested in the investigation of nitrobenzene compounds and studied first the analogue of sulfanilamide, *p*-nitrobenzenesulfonamide. This compound, when tested with streptococci and pneumococci, showed a high bactericidal value but had such toxicity that its clinical employment was not undertaken. With the appearance of sulfapyridine and sulfathiazole, the nitro analogues, 2-(*p*-nitrobenzenesulfonamido)-pyridine and 2-(*p*-nitrobenzenesulfamido)-thiazole, were produced and their properties studied. The studies showed that these two compounds were not readily absorbed from the intestines, an observation which suggested their use in intestinal infections. As the compound 2-(*p*-nitrobenzenesulfonamido)-pyridine was less readily absorbed, its effects on a patient suffering with ulcerative colitis were studied, with results so encouraging that we began a systematic study of its effects in chronic idiopathic ulcerative colitis. For purposes of simplification, 2-(*p*-nitrobenzenesulfonamido)-pyridine was called Nisulfadine, and 2-(*p*-nitrobenzenesulfamido)-thiazole was called Nisulfazole. (Fig. 1.)

Our first report was in 1942¹ and included five cases; all the patients were treated with both compounds and showed encouraging results. A second report² in 1944 included

fifteen patients and a third report,³ which included patients seen up to 1946, describes twenty-one cases. The present paper includes thirty-seven patients who have been followed the past five years.

We realize the criteria for the diagnosis of chronic ulcerative colitis are not as clear as we might desire. The causative factor or the causative organism is uncertain, so there cannot be the convincing demonstration of an etiological agent such as the *Entamoeba histolytica* in amebic dysentery, or the *Bacillus dysenteriae* in acute or chronic dysentery. The absence of these organisms in all cases, however, removes two large groups of chronic dysenteries from consideration.

All of the cases treated were diagnosed chronic ulcerative colitis after proctoscopic examination showed the presence of ulcers and the x-ray showed the characteristic picture of "feathering" of the walls of the intestine, loss of haustration and the presence of the characteristic "garden hose" type of colon.

Anemia of the secondary type was a very common finding in our patients before treatment. Eighteen of the thirty-seven patients showed a red cell count below 4,000,000, twenty-six showed a hemoglobin below 80 per cent (12.4 Gm.). Five patients showed a red cell count below 3,000,000, eleven patients showed a hemoglobin below 60 per cent (9.5 Gm.). The lowest red cell count was 2,650,000, the lowest hemoglobin 35 per cent (5.5 Gm.). The severe anemia

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so frequently seen in our patients apparently was not caused by the loss of blood since some of the patients having the most severe anemia passed only insignificant amounts of blood. There seems to be a definite tendency in this disease to develop anemia. Many patients followed after dismissal from the hospital showed a persistent tendency to develop anemia although the diarrhea had been checked and the stools had become normal.

In contrast to the anemic group, the patients with red cell count above 4,000,000 outnumbered those below, although only eleven of the thirty-seven patients showed a hemoglobin above 80 per cent. The patients without a severe secondary anemia usually made a more rapid and more lasting recovery. The patients who had the most severe diarrhea usually showed the greatest degree of anemia although one patient who, on admission, had fifteen stools in twenty-four hours showed a red blood count of 4,730,000, hemoglobin 87 per cent (13.5 Gm.), and another patient who had twelve stools daily showed a red blood count of 4,500,000, hemoglobin 81 per cent (12.5 Gm.).

Chopra and Chakravarty⁴ found gastric hypochlorhydria very frequent in chronic ulcerative colitis. This point was investigated in twenty of our patients, employing the alcohol test meal which was also used by Chopra and Chakravarty. We employed the four-test fractional meal and found that, according to Napier's classification, only two patients showed hyperacidity above 65 in any specimen. The other patients showed either a low normal, 10 to 25, or achlorhydria. Our interpretation of the results of the gastric analyses is that the gastric acidity is quite variable or even absent in chronic ulcerative colitis.

Our studies in this series of patients have added nothing to our concepts of the etiology of this disease. The stool cultures

showed only the normal bacterial inhabitants of the intestinal tract. Many of the patients showed some degree of emotional instability but the percentage was not higher than that seen in a routine check of hospital patients. In some patients, emotional upsets undoubtedly aggravated the patient's condition, but we have had the same experience repeatedly in patients with cardiac disease, with arterial hypertension and with lobar pneumonia. The mental state aggravates the patient's condition in a variety of diseases. There is certainly a mental factor in ulcerative colitis; and while we cannot agree with the inclusive title of Daniels's paper, "Non-specific Ulcerative Colitis as a Psychosomatic Disease,"⁵ we readily agree with his conclusion that "A carefully taken psychosomatic history should be included in all cases of ulcerative colitis."

Because of the suggestion that chronic ulcerative colitis might possibly be a form of lymphogranuloma venereum, Frei tests were performed on all patients. Only one showed a faintly positive reaction, which is additional confirmation of the statement of Rodaniche, Kirsner and Palmer⁶ that the virus of lymphogranuloma venereum is "in no way involved in the great majority of cases."

The ages of our patients varied between six years and seventy-one years. Grouped into decades, the first decade comprised thirteen cases, the second decade seven cases, the third eight, the fourth three, the fifth four, the sixth and seventh two cases.

The duration of the disease showed great variation, from one month to eighteen years. Seven cases had a duration of less than six months; twenty-five cases had a duration greater than one year. The most prompt response to treatment, as one might anticipate, appeared in the patients showing the lowest chronicity; these patients also showed the most permanent results.

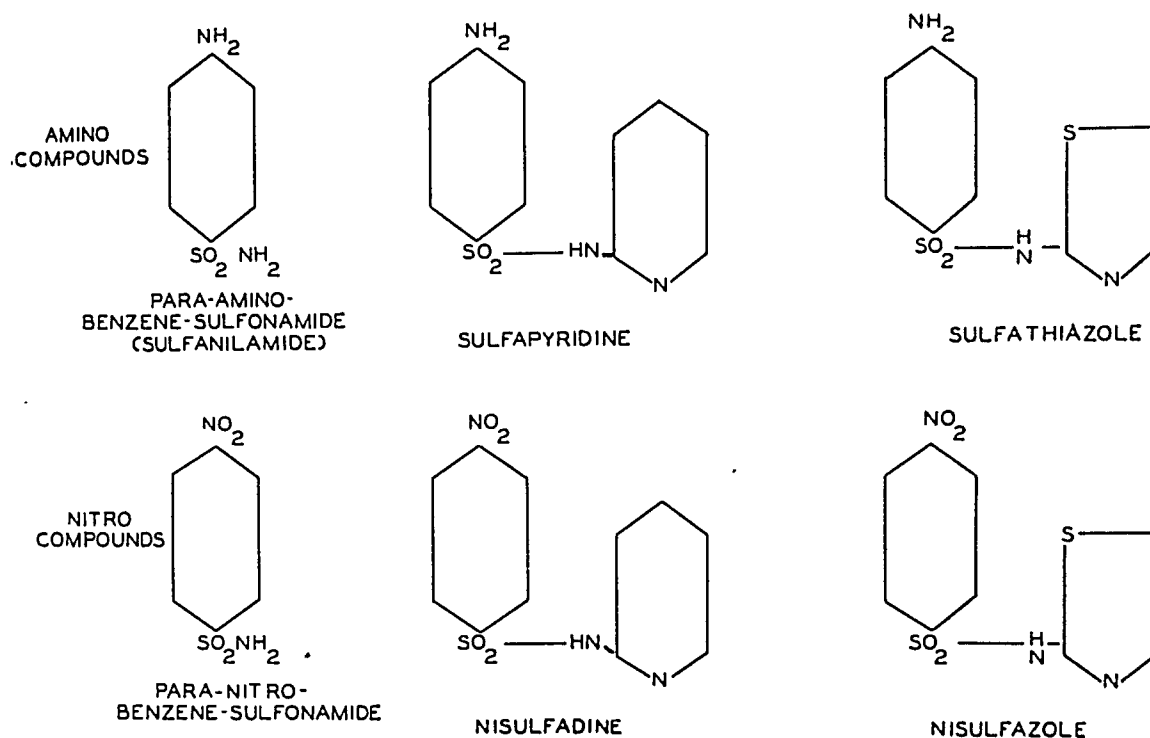


FIG. 1. Amino and nitro compounds.

The general treatment of the patients followed the lines usually recommended in the treatment of this disease. The patients were placed on a bland, residue-free diet and encouraged to partake freely of fluids. If the patient had lost much fluid from watery evacuations, subcutaneous normal saline infusions were administered. If the patient had very frequent stools, laudanum or paregoric was administered; and if they suffered from tenesmus, belladonna or traserin was employed. Patients showing marked anemia were given blood transfusions.

Nisulfazole was administered in the early cases only by mouth, either in tablets, capsules or enteric coated tablets. The enteric coated tablets were employed in patients who developed nausea, but often proved unsatisfactory as patients who had a very active diarrhea often passed these tablets undissolved. The initial dose by mouth varies from 4 to 6 Gm. in twenty-four hours. If nausea developed, the drug was withdrawn for twenty-four hours and then medication was resumed with a dosage of 2 or 3 Gm. daily.

Nisulfazole, when administered by mouth, is partially transformed into sulfathiazole and both compounds appear in the blood. Table I shows a typical example.

TABLE I
NISULFAZOLE AND SULFATHIAZOLE BLOOD LEVELS
R. T., age 19, No. 4 of Table II

	Mg. per 100 cc. of Blood		Dosage of Nisulfazole
	Nisulfa-zole	Sulfa-thiazole	
2/27/42	8.8	1.4	4 Gm. daily in 4 equal doses
3/3/42	9.1	1.5	
3/6/42	9.6	1.4	
3/11/42	9.2	1.15	
3/13/42	9.8	1.7	
3/18/42	8.6	1.5	
3/21/42	6.6	0.7	
3/24/42	10.5	2.5	6 Gm. daily in 4 equal doses Drug discontinued because of nausea
3/27/42	11.8	1.4	

The degree of absorption as measured by the blood values varied in different patients. Thus one patient, No. 5, on a daily dosage of 3 Gm. of nisulfazole, showed blood

Nisulfazole in Ulcerative Colitis—*Major*TABLE II
SUMMARY OF RESULTS

	Age	Sex	Duration	Admitted	No. Stools Daily on		Length of Treatment in Hosp.	Result on Dismissal	Relapse	Remarks
					Admission	Dismissal				
1	71	M	18 mo.	6/23/41	10	2	1 mo.	Recovery	None	Died "heart attack" (coronary occlusion?) 10/19/43
2	16	M	4 mo.	6/30/41	18	2	3 wk.	Recovery	One slight	Died pneumonia 1/18/44
3	23	M	14 mo.	7/28/41	14	2	5 mo.	Recovery	Two slight	Markedly improved 6/20/46. Rarely has symptoms. No medication for 2½ yrs.
4	19	F	9 mo.	1/19/42	10	2	4 wk.	Recovery	One slight	"Well" 11/23/45. No medication for 2 yrs. Has gained 20 lbs. Normal x-ray 7/1/42
5	22	F	5 mo.	2/13/42	27	3	2 mo.	Recovery	None	Died later, cause unknown; no diarrhea
6	19	M	30 mo.	7/23/42	8	3	3 mo.	Improved	Two	Died at home 12/21/44 (pneumonia?)
7	37	F	12 mo.	8/4/42	20	2	10 wk.	Recovery	None	"Well" 6/20/46. No medication for 1 yr. Has gained 53 lbs. Normal x-ray 5/15/45
8	18	F	6 yr.	1/16/43	7	1	1 mo.	Recovery	None	"Well" 1/14/44. No medication for 2 yrs.
9	54	M	3 yr.	1/19/43	18	2	4 mo.	Improved	None	Improved 6/20/46. No medication for 2 yrs. Colostomy 3/8/43
10	40	M	5 mo.	8/2/43	8	2	1 mo.	Recovery	None	"Perfectly well" 6/20/46. No medication for 1 yr. Normal x-ray 6/24/44
11	41	F	1 mo.	10/24/43	10	1	10 wk.	Recovery	None	"Well, feeling fine" 5/18/45. No medication for 1 yr.
12	37	F	4 mo.	3/14/44	6	1	3 mo.	Recovery	None	"Well" 6/20/46. No medication for 1 yr. Has gained 30 lbs. Normal x-ray 5/24/44
13	13	M	5 yr.	8/22/44	12	2	1 mo.	Recovery	One slight	Symptom-free 6/20/46. No medication past six months
14	30	F	3 yr.	10/22/44	15	2	2 mo.	Recovery	None	"Well" 10/2/45. No medication for 1 yr. Nearly normal x-ray 12/21/44
15	18	F	7 mo.	10/31/44	18	1	2 mo.	Recovery	Two slight	Symptom-free 5/18/46
16	27	F	4 yr.	11/25/44	20	2	4 mo.	Recovery	None	Symptom-free 6/20/46. Complicated by intestinal polyposis. Colectomy planned
17	14	M	10 yr.	1/24/45	8	2	3 wk.	Recovery	None	"Well" 6/20/46. No medication for 1 yr.
18	55	M	18 yr.	3/1/45	8	2	6 wk.	Recovery	One slight	Improved 7/10/46. Nisulfazole medication continues
19	24	F	12 yr.	3/10/45	7	2	1 mo.	Recovery	None	Symptom-free 7/10/46. Nisulfazole medication. Permanent stricture
20	44	M	11 yr.	4/14/45	4	1	2 wk.	Recovery	None	Symptom-free 7/25/46. Nisulfazole medication
21	6	M	1 yr.	5/25/44	4	1	6 wk.	Recovery	One	Symptom-free 6/3/46. Nisulfazole medication
22	53	M	2 mo.	7/14/45	8	1	1 mo.	Recovery	None	"Well" 6/20/46. No medication for 6 mo.
23	13	M	2 yr.	8/2/45	5	1	2 wk.	Recovery	None	Well

TABLE II (Continued)

	Age	Sex	Duration	Admitted	No. Stools Daily on		Length of Treatment in Hosp.	Result on Dismissal	Relapse	Remarks
					Admission	Dismissal				
24	13	M	6 yr.	10/27/45	6	1	6 wk.	Recovery	None	Symptom-free 6/20/46. No medication for 3 mo. Stricture of descending colon
25	53	M	3 yr.	11/14/45	3	1	2 wk.	Recovery	None	Symptom-free 6/20/46. Nisulfazole medication
26	24	M	3 mo.	11/28/45	5	1	1 mo.	Recovery	None	Symptom-free 6/20/46. Nisulfazole medication
27	32	F	7 mo.	12/17/45	20	1	5 wk.	Recovery	None	Symptom-free 6/20/46. Nisulfazole medication
28	28	M	11 yr.	12/31/45	15	1	6 wk.	Recovery	None	Symptom-free 6/15/46. Nisulfazole medication.
29	33	M	2 yr.	12/31/45	5	1	1 wk.	Recovery	None	Symptom-free 7/10/46. Nisulfazole medication
30	14	M	9 yr.	1/18/46	10	1	3 mo.	Recovery	One	Symptom-free 6/6/46. Nisulfazole medication
31	69	F	2½ yr.	2/27/46	4	1	6 wk.	Recovery	None	Symptom-free 6/10/46. Nisulfazole medication
32	35	M	5 yr.	4/23/46	3	1	3 wk.	Recovery	None	Symptom-free 7/10/46. Nisulfazole medication
33	19	M	6 yr.	4/27/46	4	1	1 mo.	Recovery	None	Symptom-free 7/13/46. Nisulfazole medication
34	32	F	6 yr.	6/2/46	8	1	2 wk.	Recovery	None	Symptom-free 7/25/46. Nisulfazole medication
35	32	M	6 yr.	4/18/46	8	2	1 mo.	Recovery	One	Symptom-free 7/13/46. Nisulfazole medication.
36	27	M	8 yr.	6/30/46	12	3	2 wk.	Improved	None	Two normal stools daily Improved 7/18/46. Nisulfazole medication
37	7	M	3 yr.	11/26/45	10	1	1 mo.	Improved	One	Improved 7/15/46. Nisulfazole medication

values for nisulfazole of 8.3 and 7.6 mg. per 100 cc. and for sulfathiazole of 0.9 mg. and 0.7 mg.; while another patient, No. 31, on the same dosage showed values for nisulfazole of 1.82 mg. and 0.88 mg. with no sulfathiazole present.

The relationship between the blood levels for nisulfazole and the appearance of nausea showed much variation. Some patients with a nisulfazole blood level of 9 mg. per 100 cc. showed no nausea while other patients developed nausea with a blood level of 5 mg. per 100 cc.

Later the drug was administered by rectum in pectin suspension, two or three instillations of 10 cc. of a 10 per cent suspension. This method of administration

was equally effective and had the advantage of producing no nausea. While patients receiving nisulfazole only by mouth showed nisulfazole blood levels varying from 1.5 to 16.3 mg. per 100 cc., patients who received the drug by rectum in the same dosage rarely showed more than a faint trace of nisulfazole in the blood.

In looking over the summary of results obtained during the hospitalization of these patients (Table II), thirty-four of the thirty-seven cases are described as "recovered" while three are markedly improved. By "recovery" we mean that the patients were symptom-free and not passing more than two or three normal appearing, well formed stools daily. That these patients were not all

“well” is obvious from the fact that on dismissal the x-ray picture of the intestine still showed lack or diminution of the normal haustration and that ten of them subsequently suffered from relapses of varying degrees.

The causes of these relapses were not always clear. The most common cause assigned by the patients was dietary indiscretions. In two instances, however, relapse was accompanied by purulent maxillary sinusitis, in one patient by acute mononucleosis, in one patient by acute pyelitis and in one patient by erythema nodosum.

Under the caption “remarks,” we have summarized the latest reports we have received from the patients. Where the term “well” is employed, it signifies the patient’s own description. “Symptom-free” is employed to mean that the patient does not pass more than two stools daily, that the stools are normal in appearance and that no blood is evident.

It is also apparent that some of the patients described as “symptom-free” are still taking nisulfazole and some have taken it for a considerable period. No. 19 has taken nisulfazole in doses of 2 Gm. daily for seventeen months, while No. 21 has taken it in the same dosage for twenty-six months, and several other patients have taken it for several months after leaving the hospital. We have not seen any untoward effects following such long administration but have insisted that such patients remain under continued observation so that frequent blood counts and urinalyses can be carried out.

The mechanism of action of nisulfazole is not understood any better than the etiology of ulcerative colitis. Presumably the action is bacteriostatic. It has been suggested that the action of nisulfazole is due entirely to the fact that it is broken down in the intestinal tract into sulfathiazole and that its therapeutic effects are

due to sulfathiazole. We believe this to be incorrect for we have been unable to obtain the same results with sulfathiazole or, for that matter, with any para-amidobenzenesulfonamide compounds. During the war we were frequently unable to obtain nisulfazole and were forced to substitute in its place sulfathiazole, sulfapyridine, sulfadiazine and sulfamerazine. None of these compounds produced the same results, a difference promptly noticed by the patients themselves. It should also be noted that the patients we have treated with nisulfazole had almost without exception previously been treated with all the usual sulfonamide compounds and several had received penicillin and streptomycin without any favorable results.

We wish to point out that a survey of Table II shows that all the patients without exception have improved with nisulfazole therapy.

We wish again to repeat the concluding sentences of our paper published in 1944: “In a disease such as chronic ulcerative colitis, a disease noteworthy for its chronicity and its tendency to recurrence, it would be hazardous to assert that most of these patients are permanently cured. We do feel, however, that therapy with nisulfazole has given us better results than any other treatment with which we are familiar.”

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Rôle of Hyaluronidase in Human Infertility*

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PROGRESS in the study of human infertility is a slow process. Occasionally, the impetus to a better understanding of the problem and to new therapeutic applications comes from observations which would seem to be entirely unrelated.

The cementing material of connective tissues is composed of substances known as mucopolysaccharides. Two such substances forming the extracellular ground substance of connective tissue are hyaluronate and chondroitin sulfate. The mucopolysaccharides are also found in the secretions of mucous membranes and glands. Karl Meyer in a recent review (1945) defines mucopolysaccharides as polysaccharides* which contain hexosamine as one component, occurring either in free form or obtained by chemical degradation from substances of higher molecular weight. The mucopolysaccharide with which we are here concerned is hyaluronic acid (or its salt, a hyaluronate). Hyaluronic acid was isolated by Meyer and Palmer (1936) from vitreous humor and umbilical cords. It is the simplest of the acid mucopolysaccharides, being made up of equimolar parts of acetyl glucosamine and glucuronic acid. It can be extracted from tissues with water and forms extremely viscous solutions if it has been prepared without the use of alkali or precipitation by glacial acetic acid. Hyaluronic acid has also been isolated from tumors and from group A hemolytic strepto-

cocci (Seastone, 1943). Meyer (1938) found that hyaluronic acid is co-precipitated with proteins in dilute acid. This reaction forms the basis for a test to be described below.

Hoffman and Duran-Reynals (1930) and McClean (1930) noted the existence in mammalian testes of factors which profoundly modify the permeability of connective tissue by their action on hyaluronic acid and later work established the wide distribution in nature of similar factors, which they found to be enzymic in character. Such factors were observed in bacteria by Duran-Reynals (1933) and by McClean (1936); in malignant tissue by Duran-Reynals and Stewart (1931) and by Boyand and McClean (1935); in snake venom by Duran-Reynals (1939); and in leeches by Claude (1937). Mann and Lutwak-Mann pointed out in a recent review (1944) that these observations give insight into the mechanism of the invasive power of certain virulent bacteria; they explain the reasons for the rapid spread in the body of poisonous snake venoms; they clarify the phenomenon of reduction of viscosity in such biological fluids as the synovial fluid; and afford a new approach to better understanding of the circumstances accompanying fertilization of the mammalian egg, as well as insight into certain factors involved in the problems of human infertility.

The factors which profoundly modify the permeability of connective tissue became known as "skin spreading factors," a term which originated from experiments designed to measure *in vivo* the increase in the

* Polysaccharides are a group of carbohydrates which contain more than three molecules of simple carbohydrates combined with each other.

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permeability of the dermis. Intracutaneous injection of such factors, together with a suitable indicator, causes the spreading or diffusion of the indicator over a wide area. The most accurate method appears to be that of Bacharach, Chance and Middleton (1940) which is based upon the measurement in rabbit skin of the total area through which a preparation of diffusing (spreading) factor spreads in a given time, compared with the area of spread of a standard preparation. Humphrey (1943) recently described a method which is based on the determination of the least amount of spreading factor required to produce a 20 per cent increase in the bleb area in guinea pig skin.

The substance effecting hydrolysis of the mucopolysaccharide hyaluronic acid has been termed "hyaluronidase" by Meyer and Palmer (1934, 1936). Chain and Duthie (1939, 1940) were the first to show that fairly pure preparations of testicular spreading factor also possess hyaluronidase activity. From the evidence so far available, it seems reasonable to conclude that the factor (enzyme or enzymes) responsible for diffusion in the dermis is identical with that exhibiting hyaluronidase activity, as measured by the viscosimetric and clot prevention tests (McClean, 1943; Lythgoe and Madina-veitia, 1943).

There are two methods available for the determination of the action of the enzyme hyaluronidase on hyaluronic acid: (1) *The Viscosimetric Assay*: The action of the enzyme produces a quantitative decrease in viscosity due to the depolymerization* of hyaluronic acid. (2) *The "Mucin Clot Prevention Test"*: This is based on the fact that the addition of hyaluronic acid to acidified blood serum produces a mucin clot, an observation previously made by Karl Meyer (1938).

* The larger the molecule the greater is the viscosity of its solution. Hyaluronidase breaks up the long molecule of hyaluronic acid and thereby renders it less viscous.

When hyaluronidase depolymerizes hyaluronic acid, a clot will *not* form upon the addition of acidified serum. A recent description of the mucin clot prevention test is given by McClean (1943). It appears that the destruction of the clotting power of hyaluronic acid is an early stage in its degradation, which can be detected before any appreciable decrease in viscosity occurs.

Mann and Lutwak-Mann (1944) present the following scheme which illustrates the successive stages in the degradation of hyaluronic acid and its breakdown products.

Substrate	Active Agent	Characteristics of Reaction
Viscous hyaluronic acid	Hyaluronidase from Testes Bacteria Snake venoms	Rapid. Optimum pH 6.0 to 7.0 dependent on salts. Anaerobic, insensitive to organic solvents, antiseptics.
↓		
Depolymerized, non-viscous hyaluronic acid	Testes Bacteria Venoms	Slow.
↓		
Glucuronic acid plus N-acetyl-glucosamine		Fairly rapid. Optimum pH 7.4 to 7.8. Sensitive to organic solvents, antiseptics; aerobic in animal tissues and bee venom; anaerobic and aerobic in yeast and bacteria.
↓		
Glucosamine plus acetic acid		
↓		
Ammonia plus deamination product		

The mammalian testis possesses in addition to hyaluronidase an enzyme system which deaminates and oxidizes amino sugars. The full implication of this is not yet understood.

The hyaluronidase activity of human semen was measured by Joël and Eichenberger (1945) and by Werthessen et al. (1945) by means of the viscosimetric test. Because of the inherent difficulties of this method, we prefer to assay hyaluronidase in semen by the mucin clot prevention test.

Specific antisera can be produced in an animal by repeated injections of hyaluronidase preparations. By the addition of appropriate antisera, all activities of the enzyme can be neutralized, that is, the clot prevention, the fall in viscosity and the spreading effect in skin. These reactions are highly specific. McClean (1943) has shown that sera against bacterial hyaluronidase are species but not type-specific, and serum against diffusing factor from bull testis inhibits this enzyme but is ineffective against one made from mouse testis or derived from bacteria. Another interesting fact is the "adaptive" capacity of certain bacteria to react to the inclusion of hyaluronic acid in the medium by the production of increased amounts of hyaluronidase. McClean (1942) found that there is an inhibitor of the enzyme in the blood of the living animal, apparently linked to the pseudoglobulin fraction. Chondroitin sulfuric acid, heparin and depolymerized hyaluronic acid inhibit hyaluronidase, but glucuronate and glucosamine do not. The inhibition due to these substances is probably of the competitive type as the inhibitors are structurally similar to hyaluronic acid (Mann and Lutwak-Mann 1944). Leonard and Kurzrok (1946) have shown that blood from various species inhibits hyaluronidase when tested by the dispersion of follicle cells surrounding recently ovulated rat ova.

The problem of immediate concern is the part played by hyaluronidase in fertilization. McClean and Rowlands (1942) made the very interesting observation that hyaluronidase is capable of dispersing the follicle cells which surround recently ovulated mammalian ova. The follicle cells that surround the mammalian ovum are embedded in a transparent viscous gel which must be removed before the sperm can penetrate the egg. Hyaluronidase prepared from various sources (testes, bacteria, snake venom) was allowed to act on the recently

ovulated ova. The follicle cells were dispersed without dissolution until the egg was left completely denuded. The enzyme action was found to be restricted apparently to the liquefaction of the gel (which probably contains hyaluronic acid) without affecting the ovum itself.* The authors point out that these observations could account for certain types of sterility as being due either to an insufficient concentration of hyaluronidase, as in instances of low sperm count, or else to an actual deficiency in the formation of the enzyme by the male organism. Eckete and Duran-Reynals (1943) confirmed the dispersing effect of hyaluronidase on the follicle cells surrounding the mouse ovum. Leonard and Kurzrok (1945) corroborated the observations on rat ova.

Rowlands (1944) reported a most significant observation. In a series of experiments on rabbits he determined the approximate number of sperm necessary for fertilization. For maximum fertility one million or more sperm are required, while 100,000 sperm are incapable of fertilization. He prepared a sperm-free, hyaluronidase-containing filtrate from two million sperm. He then artificially inseminated rabbits (previously ovulated by means of chorionic gonadotrophin) with sperm concentrations known to be inadequate for fertility, but added to the semen the hyaluronidase-containing filtrate of sperm. In four out of five experiments the added hyaluronidase filtrate permitted fertilization to occur.

The observations of Rowlands, and McClean and Rowlands led us to apply their results to certain problems of human infertility. Is there a direct relationship between sperm concentration in man and the amount of hyaluronidase in semen? Do normal semen specimens, that is, normal as to sperm population (100 million or more

* Leonard and Kurzrok observed that the enzyme papain dispersed the follicle cells of the rat with equal rapidity, but at the same time seemed to damage the ovum.

per cc.), morphology, motility, etc., always contain hyaluronidase? Is the amount of hyaluronidase necessary to dissolve the gel about the follicular cells always the same, or do gels vary as to their content of hyaluronic acid? Do some sterile women exhibit antibodies to hyaluronidase? What are the best methods of utilizing hyaluronidase clinically? Can one utilize antibody formation against hyaluronidase as a method of inducing sterility? How is hyaluronidase transported by sperm? Is there a selective secretion of hyaluronidase by the Fallopian tubes? What is the effect of the menstrual cycle? Our observations give us only a partial answer to some of these problems and lead to speculation about the others.

EXAMINATION OF SEMEN

Sterile glass containers are supplied and instructions given to collect the specimens in the morning and bring them to the office within two hours. Condom specimens are not accepted. The following is the routine procedure:

1. Measurement of semen volume.
2. Motility rating. Motility is estimated by the standards of Lambert and McKenzie (1940). A small drop of semen is placed on a slide with a cover glass and the specimen is observed at room temperature using a microscope with a magnification of 400 diameters. The motility observed is designated as 0, +1, +2, +3, +4 or +5. The +5 denotes maximum motility.
3. Percentage of motile spermatozoa. The percentage of motile spermatozoa is determined by covering a small drop of semen with a glass cover slip and examining it under the microscope at 400 diameters magnification after warming to body temperature. Several fields are examined and the percentage of motile sperm determined. Another method for determining the percentage of motility is the staining procedure of Hammen (1944) using brilliant cresyl

blue and gum arabic. In this procedure the motile sperm will be colored blue-purple and the non-motile sperm will not be colored. We believe, however, that in view of the time (at least one hour) consumed in staining, the accuracy is not great enough to warrant its use routinely.

4. Percentage of abnormal spermatozoa. Using both $\times 400$ magnification and oil immersion ($\times 1350$), the percentage of cells that are not perfectly normal is estimated. The abnormalities include embryonal forms, angulated sperm, headless sperm, tailless sperm, sperm with misshaped heads, macro heads, micro heads, cytoplasmic collars, double headed sperm, double tailed, and pin-headed sperm. A fairly accurate determination can be made by counting the number of abnormal cells present in counts of 10 cells each, and averaging five such counts taken in different fields of the slide.

5. Concentration counts. The concentration of spermatozoa (number per cc.) was determined by means of a hemacytometer with a Neubauer counting chamber in the following manner: The semen is stirred with the white cell pipette and is then sucked into the pipette to the 0.5 mark, or to the 1 mark if the count on superficial examination appears to be low. The tip of the pipette is wiped and the diluting fluid is sucked up to the 11 mark. (For the diluting fluid use 5 cc. saturated NaHCO_3 to 95 cc. of 1 per cent formalin.) The pipette is shaken thoroughly. The counting is done in the same way that red blood cells are counted (i.e., 5 squares). The final figure is multiplied by 1,000,000 if the dilution is 1 to 20 (i.e., the semen was taken up to the 0.5 mark); or the final figure is multiplied by 500,000 if the dilution is 1 to 10 (i.e., the semen was taken up to the 1 mark).

6. Hyaluronidase assay. The method of determining hyaluronidase in semen is based

on the fact that a clot is formed when hyaluronic acid is combined with acidified serum proteins (blood serum). When hyaluronidase acts on the hyaluronic acid, however, the clot does not appear upon the subsequent addition of acidified blood. The hyaluronic acid is depolymerized and split by the enzyme into simpler products which do not give a precipitate or clot. If hyaluronic acid is layered carefully over acid serum, a distinct white ring will form immediately at the interface. In the presence of hyaluronidase a ring will not form, and the interphase as well as the layers will remain clear.

I. Preparation of Buffers:

Solution 1. *Acetic acid* 0.5M—30.015 Gm. CH_3COOH made to a liter with distilled water.

Solution 2. *Sodium acetate*—68.035 Gm. $\text{NaC}_2\text{H}_3\text{O}_2 \cdot 3\text{H}_2\text{O}$ /liter distilled water.

Solution 3. *Acetate buffer* 0.1M; pH 6.0—1 cc. solution 1 plus 20 cc. solution 2. Take 20 cc. of the mixture, dilute to 100 cc. with distilled water.

Solution 4. *Acetate buffer* 0.5M, pH 4.2—28 cc. solution 1 plus 10 cc. solution 2.

II. Preparation of Materials:

1. *Substrate*. Na-hyaluronate 0.025 Gm. is completely wetted with two or three drops of glycerine, and is dissolved in 10 cc. of 0.1M acetate buffer at pH 6.0. The hyaluronic acid dissolves slowly, so constant stirring with a glass rod is necessary. This solution is kept in the ice-box until needed, at which time it is brought to room temperature. (1 cc. = 2.5 mg.)

2. *Enzyme*. Hyaluronidase 0.025 Gm. is dissolved in 10 cc. of 0.1M acetate buffer at pH 6.0. This solution should not be kept more than two to three hours.

3. *Acidified Serum*. 10 cc. of human blood collected anerobically,* is centrifuged after

having been allowed to stand undisturbed for one-half hour. Five cc. of the clear serum is added to 45 cc. of 0.5M acetate buffer at pH 4.2. The serum is acidified to pH 3.1 with approximately 1.4 cc. of 4M HCl (Seastone, 1943).

4. *Semen*. One cc. of human semen, collected $\frac{1}{4}$ to five hours before use, is added to 0.1M acetate buffer at pH 6.0. The amount of acetate buffer added depends on the dilution of semen desired.

III. Apparatus:

1. *Micro-Boerner Centrifuge Filter*. The Boerner filter* is essential to the test. Semen is a turbid suspension and the ring cannot be seen unless the semen is filtered. In ordinary filtration methods there is a large percentage of loss when 1 cc. of the material is filtered. The Boerner filter is a modification of the Seitz filter, using centrifugal force instead of suction. It is composed of two parts: a base which holds the filter paper, and a cylinder which is screwed into the base (Boerner 1942).

2. *Layering Tube*. For the purpose of layering the solutions with the least amount of effort and disturbance we have found the following arrangement to be of great help. A 10 cc. centrifuge tube is held in an inclined position (about 35°) by a clamp attached to a ring-stand. The bottom of the centrifuge tube is packed with cotton to prevent breakage. It is advisable to put in sufficient cotton so when the Kahn tube is placed within the centrifuge tube the mouth of the Kahn tube protrudes slightly. This facilitates removal of the tube.

IV. Procedure:

1. One-half cc. of substrate (Na hyaluronate 1.25 mg.) is added to test tubes a, b, c, d, and e containing the following:

Tube a—1 cc. undiluted semen

Tube b— $\frac{1}{2}$ cc. undiluted semen

*For this procedure see: PETERS, J. P. and VAN SLYKE, D. D. *Quantitative Clinical Chemistry*. Vol. II, chap. II. Baltimore, 1932. Williams & Wilkins Co.

*This filter and filter pads can be purchased from the Arthur H. Thomas Company, Philadelphia, Pennsylvania.

Tube c— $\frac{1}{2}$ cc. of the diluted semen (0.25 cc. semen plus 0.25 cc. acetate buffer pH 6.0)

Tube d— $\frac{1}{2}$ cc. buffer (0.1M acetate pH 6.0)

Tube e—1 cc. hyaluronidase solution

2. The contents of the test tubes a, b, c, d, and e are mixed with *separate* stirring rods and are placed in the incubator or water-bath at 37.5°C. for one hour.

3. The turbid solutions are filtered through micro-Boerner centrifuge filters into Kahn precipitation tubes at 2200 RPM for twenty-five minutes. The filtrate is clear and may contain hyaluronic acid or depolymerized hyaluronic acid, and the split products, but does not contain spermatozoa.

4. The Kahn tube containing the filtrate is placed in the layering tube. One cc. of the acidified serum is carefully layered on 1 cc. or less of the clear filtrate. If the specific gravity of the filtrate is not high enough to support the acidified serum, the procedure can be reversed, the filtrate being layered on the acidified serum. At the interface of the two liquids a white ring will appear *immediately* if hyaluronidase is absent or present in insufficient concentration. In the presence of sufficient hyaluronidase a ring will not be formed. Usually the ring (or mucin clot) will appear immediately. The ring will vary in intensity according to the amount of hyaluronic acid unacted upon by the enzyme. The greater the depolymerization the less the ring; with complete depolymerization there is no ring. Occasionally, the ring will not appear for sixty seconds. If the ring appears at the end of five to ten minutes and is faint in appearance, it implies that the amount of hyaluronidase is just about sufficient to depolymerize the available hyaluronic acid.

We have attempted to establish a hyaluronidase unit for semen, based on the action of a purified hyaluronidase on fairly pure hyaluronic acid. For purposes of con-

venience in handling, we chose a concentration of 2.5 mg. of hyaluronic acid per cc. as our substrate. The amount of the most highly purified enzyme preparation needed to depolymerize 2.5 mg. of hyaluronic acid was approximately 2.5 mg. It can be readily seen that such a unit would vary with the purity of both substances. We found that semen specimens containing 100 million sperm per cc. and which contained hyaluronidase, exhibited an activity sufficient to depolymerize 2.5 mg. of hyaluronic acid. Hence, our hyaluronidase unit for semen (H.U.S.) is that amount of enzyme in 1 cc. of semen sufficient to depolymerize 2.5 mg. of hyaluronic acid under the conditions of the experiment. If 2 cc. of semen are required to depolymerize 2.5 mg. of hyaluronic acid, the specimen contains 0.5 H.U.S. per cc. If 0.5 cc. of semen is required, the specimen contains 2 H.U.S. per cc. of semen. If the amount of semen is inadequate, we may use 0.5 cc. of semen acting upon 1.25 mg. of hyaluronic acid.

COMMENTS

Table I represents a study of ninety semen specimens derived in the main from infertile couples. Four cases of repeated miscarriage are also included. The concentration of hyaluronidase in semen increases with the sperm population. This is also borne out by Graph A. This confirms the findings of Joël and Eichenberger (1945) and Werthessen et al. (1945). The critical point appears to be at 50 million sperm per cc. Below this level practically no hyaluronidase can be found in the semen, except in specimens Nos. 370, 438, 359 and 411. The concentration of hyaluronidase definitely increases as the sperm population exceeds 50 million per cc. It is interesting to correlate this fact with the clinical observation held for many years that specimens below a sperm concentration of 50 million per cc. have a very low fertility value.

TABLE I

Series 1946		Sperm Concentration Million/ cc.	H-ase Units	Motility		Morph- ology Per Cent Ab- normal	Approx. Age of Spec. Hr.	Clinical Notes
Case No.	Spec. No.			Degree	Per Cent Motile			
1	341	0	0	0	0	0	1	P. Entirely normal*
2	346	0	0	0	0	0	Office	P. † Wife not seen; injury to testes as child
3	416	0	0	0	0	0	3	P. Hypogonadism of husband
4	435	0	0	0	0	0	3	P. Gravid with previous husband but miscarried
5	327	1	0	5	99	5	Office	S. ‡ Right cystic ovary study not complete; tubes patent under 120. Pruritus of scrotum—treated with x-ray
6	339	1	0	5	50	40	1	Same as case No. 5
7	401	1	0	5	85	30	Office	P. Incomplete§
8	342	2	0	5	70	20	Office	S. Mild genital hypoplasia, otherwise entirely normal
9	379	2	0	Oscillation		80	2½	P. Biopsy normal, tubes closed
10	334	3	0	4	15	30	Office	P. Wife not seen
11	373	4	0	5	10	90	Office	P. Acute antifixion of uterus, cervical and vaginal hypoplasia
12	397	8	0	0	0	30	Office	S. Repeated misc. (3); fundal hypoplasia
13	360	10	0	5	70	30	Office	Same as No. 8
14	438	13	.17	3	30	35	3	P. Incomplete
15	365	15	0	4	30	50	2	Same as No. 14
16	390	16	0	4	25	50	5	S. Entirely normal
17	395	20	0	4	20	70	4½	Same as No. 11
18	357	25	0	5	45	15	2	S. Entirely normal
19	359	25	.38	4	30	25	3	S. Prolongs estrogen phase, inadequate luteinization, hypothyroidism
20	411	25	.17	4	50	35	2	S. Repeated miscarriage fundal hypoplasia
21	326	30	0	5	35	70	1½	P. Tubes patent at 180 otherwise entirely normal
22	404	30	0	5	25	25	2	S. Small fibroid otherwise normal
23	344	31	0	5	80	20	1	P. Genital hypoplasia, progestational endometrium with cystic tendency otherwise normal
24	370	36	.75	5	25	25	Office	P. Mild genital hypoplasia
25	432	38	0	0	0	50	2	P. Incomplete
26	362	40	0	2	20	50	3	P. Genital hypoplasia
27	340	41	0	5	45	40	2½	Same as No. 19
28	391	42	0	5	70	35	1	P. Mild genital hypoplasia, tubes patent with antispasmodic
29	355	42	0	4	30	60	5	P. Congenital retroversion, cervical hypoplasia
30	394	43	0	4	30	45	5	Same as No. 26
31	Pl.	45	0	4	40	50	2	P. Mild fundal hypoplasia
32	4-23	45	0	3	40	50	5	S. Mobile retroversion, otherwise normal
33	331	50	2	3	35	65	3½	S. Now gravid
34	429	51	.38	5	90	5	2½	P. Small intramural fibroid
35	353	51	0	4	50	45	2½	P. Entirely normal
36	372	55	>1	4	40	30	Office	P. Entirely normal
37	437	55	>67	5	75	20	Office	P. Entirely normal
38	357	57	.5	5	50	20	23	P. Entirely normal
							2	P. Right salpingo-oophorectomy; partial resection of left ovary remaining tube patent at high pressure

TABLE I—(Continued)

Series 1946		Sperm Concen- tration Million/ cc.	H-ase Units	Motility		Morph- ology Per Cent Ab- normal	Approx. Age of Spec. Hr.	Clinical Notes
Case No.	Spec. No.			Degree	Per Cent Motile			
39	415	59	0	4	50	40	2	P. Genital hypoplasia; incomplete
40	413	63	.75	5	50	20	3½	Same as No. 29
41	352	64	.75	Oscillation		30	1½	S. Hypertension, pituitary adiposity
42	371	65	>1	5	75	25	2½	P. Genital hypoplasia; fibroid uterus, tubes patent at 170 mm.
43	399	67	.75	5	65	25	2½	S. Entirely normal
44	398	69	.75	5	60	30	2½	P. Cervical hypoplasia
45	K5-7	70	0	4	85	20	4	P. Entirely normal
46	364	73	>1	4	60	40	3	P. Tubes closed
47	374	74	.75	5	70	30	2	P. Genital hypoplasia
48	418	75	0	5	85	30	3	S. Completely normal
49	367	76	.38	5	50	30	3	P. Genital hypoplasia, old para- metritis
50	386	80	.83	3	30	65	2½	P. Uterine fibroids; inadequate lutein phase
51	366	85	0	5	85	30	1½	P. Tubes patent, old pelvic inflam- matory disease
52	361	88	1	5	90	20	1	P. Entirely normal
53	392	93	0	5	85	25	Office	P. Cervical hypoplasia
54	356	95	0	3	25	55	5½	Same as No. 33
55	406	100	.5	5	60	35	1	P. Entirely normal
56	389	101	1.5	5	60	20	2	P. Entirely normal
57	431	101	>1	5	40	60	3	P. Tubes patent, incomplete
58	333	101	2	5	85	30	Office	P. Cervical hypoplasia; acquired retroversion
59	427	110	>1	5	50	30	3	Same as No. 39
60	PE. 3-29	100†	>3	5	85	20	3	P. Entirely normal
61	424	112	1	3	35	35	4	P. Entirely normal
62	380	123	.75	5	25	35	2½	P. Moderate sec. endometrium
63	428	133	.75	5	85	15	3	P. Incomplete
64	422	133	.80	5	85	10	2½	S. Incomplete
65	MA. 4-22	134	0	5	95	10	3	Donor
66	325	136	>1	4	85	20	3	S. Repeated misc. (3); moderate genital hypoplasia, otherwise nor- mal
67	MA 64	137	.38	5	90	10	22	Same as No. 65
68	377	146	0	5	65	20	3½	Same as No. 35
69	354	146	>3	5	80	30	1½	P. Incomplete
70	387	155	1.25	5	85	20	Office	S. Pituitary adiposity, hypertension
71	414	155	0	5	75	25	2½	S. Entirely normal
72	MA 4-3	157	0	5	85	10	3	Same as No. 65
73	MAR 4-4	158	>2	5	85	25	3½	Same as No. 58
74	MA 5-1	160	>.4	5	85	10	4	Same as No. 65
75	375	164	>1	5	50	20	1½	P. Inadequate secretory endome- trium
76	385	170	1.5	5	85	15	1½	P. Small fibroid
77	434	177	>3	5	90	10	2	P. Entirely normal
78	417	187	0	5	80	40	2	P. Anovulatory cycle

TABLE I—(Continued)

Series 1946		Sperm Concentration Million/cc.	H-ase Units	Motility		Morphology Per Cent Ab-normal	Approx. Age of Spec. Hr.	Clinical Notes
Case No.	Spec. No.			Degree	Per Cent Motile			
79	396	193	0	5	85	15	5	S. Repeated misc. (3); vaginal and cervical hypoplasia; incomplete
80	368	200	>2	5	50	60	Office	P. Genital hypoplasia
81	433	201	0	5	80	80	3	S. Incomplete
82	345	205	>10	5	50	30	3	S. Entirely normal
83	430	220	>2	5	80	30	3¾	P. Incomplete
84	436	281	>3	5	85	20	3	P. Incomplete
85	335	302	>1	5	30	80	Office	P. Tubes closed, otherwise normal
86	343	310	>10	5	65	35	2¾	S. Thin proliferative endometrium; incomplete
87	369	332	2.5	4	90	30	2½	S. Repeated misc. (5); cervical hypoplasia, congenital retroversion
88	F.	363	>2	5	90	10	Office	Control
89	378	410	1.25	4	40	40	3	Same as No. 85
90	F.	468	2.2	5	90	10	Office	Control; same as No. 88

* By entirely normal we mean physical examination negative, pelvis negative, tubes patent at pressure under 140 mm. Hg., patient ovulates, endometrium good secretory phase, basal metabolism rate normal.

† Primary sterility.

‡ S. Secondary sterility.

§ By incomplete we mean that the patient has not been completely studied. Plus 5 indicates maximum motility.

Specimens with large concentrations of sperm do not of necessity have great concentrations of hyaluronidase, so that in specimens having a sperm population greater than 100 million per cc. there is no direct relationship between concentration of sperm and the amount of hyaluronidase. Patient F. (case 88) produced 362 million sperm per cc. containing > 2 H.U. in his first specimen, and 468 million sperm per cc. and 2.2 H.U. in a subsequent specimen.

Table I exhibits several interesting points. Two cases present concentrations of sperm between 90 and 100 million per cc. One would have expected to find hyaluronidase in these specimens. None was found. Specimen No. 277 (case 68) with 146 million sperm per cc. having excellent percentage motility and motility, and fairly good morphology, would ordinarily be considered a good specimen. Yet it contained no hyaluronidase. The same situation occurs in specimen No. 414 (case 71). Hence the fact that a specimen has an

adequate and even a very large sperm population does not always imply that hyaluronidase is present in the semen, and, from our present viewpoint, that it is fertile.

There appears to be no relationship between the amount of hyaluronidase and (1) sperm morphology, (2) percentage of motile sperm, and (3) motility of sperm.

Several cases listed in this group illustrate a number of interesting points. Patient Mac, a young man of robust health, has been used as a donor in cases of artificial insemination for the past three years. He was the most successful of the donors. Early in 1945 the percentage of pregnancies induced by him was reduced to zero, whereas it had formerly been 66 per cent. His semen specimen showed no demonstrable change. It was excellent according to all criteria used for evaluation of a specimen (sperm concentration, morphology, motility, semen-mucus penetration, etc.). In view of the fact that we were then working with hyaluronidase, we added

10 mg. of the enzyme to each specimen and then inseminated. We have obtained nine pregnancies since. We therefore examined his specimens for hyaluronidase during the past four months with the following results:

TABLE II

	Sperm Concentration, Million per Cc.	Hyaluronidase Units
March, 1946.....	134	0
April, 1946.....	157	0
May, 1946.....	160	> .4
June, 1946.....	137	.38

Our assumption that his specimen lacked hyaluronidase, and because of that was of low fertility, was justified by an immediate increase in the number of pregnancies upon the addition of the enzyme to his specimen, and by the actual demonstration of the absence of hyaluronidase in his semen.

Another interesting case is case 79 (spec. No. 396). The problem here is one of three repeated miscarriages. We believe that they were due to a cervical hypoplasia (Kurzrok 1946). In spite of a sperm concentration of 193 million per cc. there is no hyaluronidase in the specimen. Whether this factor is related to the problem of repeated miscarriage we do not know. A second case of three repeated miscarriage is case 12 (No. 397). Here the sperm concentration is 8 million per cc., hence the absence of hyaluronidase is to be expected. A further interesting relationship is borne out by the following cases: Case 35 (No. 353) exhibited 51 million sperm per cc. and no hyaluronidase. A second specimen gave 146 million per cc. also without enzyme. On the other hand, case 39 (No. 415) produced 59 million sperm without hyaluronidase, and a second specimen one week later 110 million sperm per cc. containing 1 H.U.S.

We are now treating patients that are sterile because of inadequate semen speci-

mens by the therapeutic administration of hyaluronidase. The cases chosen for treatment are those in which defective semen is the sole cause of sterility. All other factors and tests are normal. Of course, other criteria that are used in judging the adequacy of semen specimens, aside from sperm concentration, such as morphology, percentage of sperm motility, degree of motility, semen-mucus penetration, must not be overlooked.

We have utilized hyaluronidase in two ways:

1. *By Direct Addition to the Specimen.* The patient brings the semen specimen to the office, or the specimen is produced in the office. The latter is preferable but not always feasible. Ten to 20 mg. of hyaluronidase are added to the specimen and thoroughly stirred. The enzyme goes into solution. The enzyme does not modify the motility of the spermatozoa nor does it liquify cervical mucus, a fact previously recorded by Rowlands. The specimen is then taken up into a syringe and the cervix is sprayed. The semen is never injected into the uterine cavity. Immediately after insemination the patient is put into a steep Trendelenburg position for twenty minutes. The date chosen for the insemination is the date of ovulation as previously determined by the method of Papanicolaou and Shorr, or by such clinical signs of ovulation that may be present. Where the insemination is carried out more than once during a given cycle we inseminate two days before and after ovulation. We have never noted any allergic or pathologic phenomena from the use of hyaluronidase. The same technic was utilized in artificial insemination with an outside donor.

2. *By Direct Application to the Cervix.* In view of the fact that it is not always feasible for the patient to bring semen specimens to the office on specified dates of the cycle we utilized the second method, namely, the

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direct application of hyaluronidase to the cervix. The patient came to the office on the date of ovulation or as near to that date as possible. The cervix was exposed by means of a speculum and the surface of the cervix (but not the canal) was wiped clean. Ten mg. of hyaluronidase was then placed in a sterile watch glass. A sterile cotton applicator was inserted into the mucus of the cervical canal. By twisting the applicator in the canal small amounts of mucus will cling to the cotton. The applicator is then dipped into the enzyme which clings to the mucus, and inserted into the cervical canal. This is repeated several times until all enzyme is packed into the cervical canal. It is important not to cause bleeding from the cervical canal as it may wash out the enzyme or possibly inhibit its activity (Leonard and Kurzrok, 1946). The patient is then instructed to have coitus within the next few hours. This procedure is occasionally carried out three times during the cycle, two days before, during, and two days after the calculated day of ovulation.

The following cases of sterility illustrate the therapeutic use of hyaluronidase:

CASE REPORTS

CASE J. S. The patient was twenty-six years of age. She was referred to us by Dr. George Urbach. The chief complaint was a primary sterility of four years' duration. Her menses were regular and the general physical examination was negative. Pelvic examination revealed a mild cervical hypoplasia.

Insufflation on September 27, 1945, showed the tubes to be closed at a pressure of 180 mm. of Hg. The patient was advised to take Trasentine.*

* It is our custom not to make a diagnosis of closed tubes on the basis of a single test even though the pressure is run up to 180 mm. on three successive tries. Beginning with the onset of the next menstrual period the patient is advised to take six tablets of Trasentine, each 75 mg. per day, up to the mid-cycle when insufflation is again carried out. More than 50 per cent of the patients with previously closed tubes now show normal tubal patency. We believe the closure to have been due to tubal spasm. We are indebted to the late Mr. Robert Mautner of Ciba Corp. for the Trasentine.

On October 2, 1945, the insufflation test was repeated. The pressure rose to 180 mm. and dropped to 80 mm., gas passed through. Typical shoulder symptoms developed thereby implying that the tubes were patent.

On November 2, 1945, an endometrial biopsy revealed a good secretory endometrium, slightly cystic. Ovulation (Papanicolaou and Shorr) occurred on the thirteenth day of the cycle.

A semen examination on August 22, 1945, gave the following results:

Semen #P77. Age—2 hr. Volume 1 cc.

Viscosity—mucoid.

Motility—30 to 40 per cent motile. Some oscillatory motion.

Morphology—70 to 75 per cent abnormal.

Count—19 million per cc.

Another semen examination on September 21, 1946, revealed the following:

Semen #P99. Age—2 hr. Volume 2 cc.

Viscosity—mucoid.

Motility—40 per cent motile. Oscillatory motion.

Morphology—70 to 75 per cent abnormal.

Granular and cellular debris.

Count—19 million per cc.

The patient was in to see me on December 10, 1945. Her last menstrual period was November 29, 1945. This was on the twelfth day of the cycle. Ten mg. of hyaluronidase was applied to the cervix and the patient instructed to have intercourse within a few hours.

The A-Z test was positive on January 10, 1946.

CASE A. W. M. The patient was thirty-one years of age. The chief complaint was a secondary sterility of seven years' duration. She conceived immediately in 1938, miscarried at three months and then had a D and C. Her menses were regular; the general physical examination was negative. The pelvic examination showed a moderate genital hypoplasia.

On October 26, 1945, an insufflation test showed the tubes to be closed at 180 mm. of Hg. The patient was advised to take Trasentine.

On November 5, 1945, an endometrial biopsy revealed a secretory endometrium. Ovulation occurred on the fifteenth day of the cycle.

An insufflation on December 13, 1945, showed the tubes patent at 180 mm. of Hg. Typical shoulder symptoms developed. The patient was advised to take Trasentine.

On February 5, 1946, insufflation test showed tubes patent at 140 to 120 mm. of Hg. Typical shoulder symptoms developed.

The patient came in to the office on March 6, 1946. Her last menstrual period was February 22, 1946. Hyaluronidase was applied to the cervix, and she was given an injection of 2,000 R. U. Progynon B.

The patient was in again on March 27, 1946. Her last menstrual period was March 21, 1946. Hyaluronidase was applied to the cervix, and she was given an injection of 1,000 I.U. Anteron (equine gonadotrophin). The purpose of the injection was to hasten the date of ovulation, for the patient had made this visit somewhat too early in the cycle. She was advised to have intercourse within a few hours. The patient brought in a semen specimen collected two hours before her arrival at the office. Coitus was advised again on the same day even though a second semen specimen produced during the same day is apt to be of poorer quality when compared with the first.

A semen examination on October 26, 1945, gave the following results:

Semen #P142. Age—2 hr. Volume 2 cc.
Viscosity—normal.
Motility—5 per cent, plus 1.
Morphology—65 to 70 per cent abnormal.
Many embryonal forms, headless sperm, cellular debris.
Count—19 million per cc.

Another semen examination on March 27, 1946, showed the following:

Semen #P324. Age 2 hr. Volume 1.5 cc.
Viscosity—very viscous.
Motility—60 per cent motile, plus 5.
Morphology—35 per cent abnormal. Cytoplasmic residues, headless forms.
Count—128 million per cc.

On May 4, 1946 the A-Z test was positive.

The patient then brought in another specimen after she conceived. The purpose of obtaining this specimen was to determine its hyaluronidase

content, for we had previously assumed without testing that none was present. Our assumption was correct for the specimen did not contain hyaluronidase. The specimen brought in on May 20, 1946, gave the following results:

Semen #P418. Age 3 hr. Volume 1 cc.
Viscosity—viscous.
Motility—85 per cent, plus 5.
Morphology—30 per cent abnormal, misshaped heads, embryonal forms.
Count—75 million per cc.
Hyaluronidase—none present, (lowest amount tested 0.75 H.U.).

CASE K. K. The patient was twenty-nine years of age. She was referred to us by Dr. W. Phelan. The chief complaint was a secondary sterility of one year's duration. She conceived three years before and had a normal delivery. Her menses have been normal, and the general physical examination was negative. The pelvic examination showed a first degree retroversion, mobile.

On March 20, 1945, an insufflation showed the tubes to be patent at 160 to 90 mm. of Hg. Typical shoulder symptoms developed.

On March 28, 1945, an endometrial biopsy revealed a secretory endometrium. Ovulation occurred on the eleventh or sixteenth day of the cycle. The vaginal spreads were not quite clear.

An insufflation on May 9, 1945, showed the tubes patent at 90 to 60 mm. of Hg. Typical shoulder symptoms developed.

A semen test on March 29, 1945, showed the following results:

Semen. Age 2½ hr. Volume 2 cc.
Viscosity—normal.
Motility—75 per cent motile. Plus 4.
Morphology 75 per cent abnormal, embryonal forms.
Count—20 million per cc.

A semen examination on November 8, 1945, gave the following results:

Semen #P160. Age 2 hr. Volume 2.5 cc.
Viscosity—normal.
Motility—plus 1.
Morphology—75 per cent abnormal.
Count—107 million per cc.

Another semen examination on February 4, 1946, gave the following results:

Semen #P 252. Age 2.5 hr. Volume 4 cc.

Viscosity—normal.

Motility—0.

Morphology—65 per cent abnormal, embryonal forms.

Count—196 million per cc.

In view of the repeated poor motility the patient was seen by Dr. Irving Lerman within two hours after coitus; motile sperm were found in the vagina and cervix.

On March 16, 1946, the patient came to the office. Her last menstrual period was March 6, 1946. Hyaluronidase was applied to the cervix.

On April 29, 1946, the A-Z test was positive.

CASE M. S. The patient was twenty-six years of age. The chief complaint was primary sterility of four years' duration. The patient has had two previous complete studies made of her problem and all findings were normal. Studies were repeated again for verification. Physical and pelvic examinations were negative.

On February 12, 1946, an insufflation showed the tubes to be patent at 70 mm. of Hg. On March 20, 1946, endometrial biopsy revealed a secretory endometrium. On April 5, 1946, the patient was seen by me. Her last menstrual period was March 24, 1946. Hyaluronidase was packed into the cervix.

The patient came in to see me on May 23, 1946. Examination showed her to be pregnant as she had missed her April period.

A semen examination on February 12, 1946, gave the following results:

Semen #P261. Volume 3.5 cc.

Viscosity—normal.

Motility—85 per cent motile, plus 5.

Morphology—10 per cent abnormal.

Count—392 million per cc.

CASE F. J. The patient was thirty-four years of age. The chief complaint was primary sterility of four years' duration. Her menses had been regular, but she had a menstrual migraine. Previous insufflations revealed patent tubes. The general physical examination was negative. She had been taking thyroid gr. $\frac{1}{4}$ to $\frac{3}{4}$ per day, also hormone injections. The

pelvic examination showed mild genital hypoplasia and a congenital retroversion.

A basal metabolism test on January 23, 1946, gave a minus 11 per cent result. The thyroid was increased to gr. 1 per day.

On January 23, 1946 a semen examination gave the following results:

Semen #P 230. Age 2 hr. Volume 2.0 cc.

Viscosity—normal.

Motility—35 per cent motile, 3 plus.

Morphology—60 per cent abnormal, embryonal forms.

Count—112 million per cc.

On February 7, 1946, an endometrial biopsy revealed a secretory endometrium. Ovulation occurred on the fifteenth day of the cycle.

The patient was in to see me on March 28, 1946. Her last menstrual period was March 18, 1946. She was given 1,000 I.U. Anteron (equine gonadotrophin), and 500 I.U. Follutein (chorionic gonadotrophin) to hasten ovulation. Hyaluronidase was packed into the cervix.

On April 25, 1946, the patient came into see me. Her last menstrual period was April 15, 1946. She was given 800 I.U. Anteron and 500 I.U. Follutein. Hyaluronidase was packed into the cervix.

On May 27, 1946, the A-Z test was positive.

CASE E. H. The patient was thirty years of age. The chief complaint was primary sterility four years' duration. The patient had had several previous examinations and numerous tests. The physical examination showed acute ante-flexion of the cervix, and a cervical hypoplasia. Tubes were previously found patent, therefore an insufflation was not done.

On March 26, 1946, endometrial biopsy revealed a moderate secretory endometrium. Ovulation occurred on the twelfth day of the cycle. The slides also showed a prolonged estrogen phase.

A semen examination on March 15, 1946, showed the following findings:

Semen #P305. Age $2\frac{1}{2}$ hr. Volume 2 cc.

Viscosity—slight.

Motility—25 per cent motile, plus 3, plus 2.

Morphology—50 per cent abnormal, embryonal forms, angulated.

Count—67,000,000.

On April 6, 1946, a semen examination gave the following results:

Semen #P336. Age $2\frac{1}{2}$ hr. Volume 3 cc.

Viscosity—normal.

Motility—70 per cent motile, plus 5.

Morphology—15 per cent abnormal, angulated heads.

Count—181,000,000.

The patient came to see me on May 2, 1946. Her last menstrual period was April 21, 1946. Hyaluronidase was packed into the cervix.

On June 3, 1946, the A-Z test was positive.

One of the problems posed by these cases is the manner by which the added hyaluronidase reaches the ovum. The answer to this problem would involve the correct explanation for the mode of transport of sperm from the vagina into the tubes in the human. The simplest explanation of the latter phenomenon is that the sperm reach the ends of the tubes by their own motility. The added hyaluronidase could be absorbed on the surface of the sperm and thus reach the ovum. A second explanation offered for the sperm transport is that sperm are aspirated into the uterus and tubes by the muscular action of these organs. Hyaluronidase could be transported in the same manner. Somehow this explanation has never been accepted by gynecologists. The senior writer has conducted experiments with the human uterus both *in vivo* and *in vitro* over a period of many years and has never noted any physiological action of the uterus that would imply aspiration.

There are two other explanations that might be offered for the manner in which hyaluronidase could reach the ovum within the tube. One is absorption of the enzyme by the cervical mucosa and its selective secretion by the secreting cells in the tubal mucosa. Rosenzweig and Walzer (1943) have shown that peanut protein entered the circulation in from eight to twenty-five minutes after its application to the cervix.

The cervical mucous membrane is made up of columnar secreting epithelium, is rich in lymphatics and is covered with an alkaline secretion. Such factors favor absorption. Against this view is the inhibitory action of blood serum and possible antibody formation.

The fourth possible explanation for the concentration of hyaluronidase about the ovum is the following. Hyaluronidase carried to the ovum by the sperm initiates by its degradation of hyaluronic acid a further production of enzyme, possibly by the end products produced in this enzymatic reaction. The point of action of this initiating process may be the secretory cells of the tubal epithelium. It is worth commenting that no satisfactory explanation has been offered as to the function of these cells, except the generalized explanation that they aid in the nutrition of the ovum.

The form or manner by which hyaluronidase is held in semen is at present unknown. Is there a "bound" and a "free" hyaluronidase? Some insight into this problem is given by the following experiment. If a given semen contains no hyaluronidase, how much enzyme must be added to the semen for the latter to depolymerize a given amount of hyaluronic acid? Enzyme preparation No. 13-1811 required 2.5 mg. to depolymerize 2.5 mg. of hyaluronic acid (1 H.U.).

TABLE III

Patient	Hyaluronidase Added, Mg.	Semen, Cc.	Amount of Hyaluronic Acid, Mg.	Result
S.	2.5	1	2.5	Ring in 10 min.
B.	7.6	1	2.5	Ring
F.	12.0	1	2.5	No ring
	4.2	1	2.5	No ring
Gr.	3.4	.4	2.5	Ring
	6.0	.4	2.5	Ring
	7.8	.4	2.5	Ring

These patients had no hyaluronidase in the semen. The addition of 4.2 mg. of enzyme was sufficient to demonstrate its activity in patient F., but the addition of 7.6 mg. to semen B failed to alter the original zero titer of enzyme. Either the enzyme was neutralized by some inhibitor (heparin inhibits the action of hyaluronidase on the rat ovum, Leonard and Kurzrok unpublished) or the enzyme entered a bound state from which it was not liberated by the conditions of the experiment. In view of these findings, we are not as yet in a position to state the precise quantity of hyaluronidase that should be added to a given semen specimen. The senior author has usually added 10 mg. and occasionally 20 mg., but even the latter amount may occasionally be insufficient.

It is an interesting theoretical consideration as to what should be the order of magnitude of sperm concentration about the ovum to yield sufficient hyaluronidase to liquefy the gel around the granulosa cells and ovum. Leonard and Kurzrok (unpublished) found that with the purest preparation of hyaluronidase available, 33 gamma of enzyme were necessary in order to disperse the follicle cells completely in the rat *in vitro* under standard conditions. If we accept the theoretical possibility that the amount of hyaluronidase necessary to disperse the follicle cells around the human ovum is in proportion, then we begin to gain some insight into the necessity for the production of such a large number of sperm in a single ejaculation. (Diameter of rat ovum 70–75 micra, human $130/140$ micra. Hartman 1929.)

According to some of our published data spermatozoa represent 160 mg. of wet weight per cc. of spermatic fluid containing 100 million sperm. One cc. of spermatic fluid weighs on the average 3 G. Hence a single sperm weighs .0016 G. made entirely of protein.

require approximately 20,000 sperm to furnish 33 gamma of enzyme. If, for purposes of discussion, we assume that hyaluronidase represents only $1/1000$ of the weight of a sperm, it would follow that the ovum must be surrounded by at least 20 million sperm in order to produce an amount of hyaluronidase necessary for complete dispersal of the follicle cells. Such an assumption might explain why an ejaculate averaging 4 cc. must of necessity have better than 400 million sperm to be considered adequate. This figure is in agreement with the one derived by actual measurement of the amount of hyaluronidase in human semen and again indicates that specimens having less than 50 million sperm per cc. have a very low fertility value. The loss of sperm in their journey through the genital tract towards the ovum must also be taken into consideration.

The problem of antibodies against hyaluronidase can be considered as part of the greater problem of sperm immunity. Numerous papers have appeared in the past two years dealing with immunization against spermatic fluid and the resultant production of temporary sterility. Considerable discussion as to the validity of the results obtained, the specific antigens, and the implications of the results, has not led to further clarification of the problem. In a previous paper (Leonard and Kurzrok, 1946) we reported attempts to find inhibitory substances against bull hyaluronidase in nine sterile women. No such inhibitor was found. To determine if some types of sterility in women might be due to increased amounts of a normal or induced inhibitor (antibody to human sperm hyaluronidase) it would appear, in the light of our experiments, that hyaluronidase derived from human spermatozoa should be employed.

CONCLUSION: The results of our experiments indicate that the use of hyaluronidase derived from human spermatozoa in the treatment of pneumonias, Boston City Hospital, Massachusetts.

based on the fact that when hyaluronic acid is added to acidified blood serum a ring forms. In the presence of hyaluronidase a ring will not form. Clear seminal plasma, obtained by means of the Boerner centrifugal filter, is essential.

2. The hyaluronidase content of human semen, as studied in ninety specimens, increases directly with the sperm concentration up to the range of 100 million sperm per cc. Beyond this concentration the hyaluronidase content does not increase proportionately.

3. Semen specimens with excellent concentrations of sperm may not contain any hyaluronidase. We consider such specimens infertile.

4. The hyaluronidase content of semen does not appear to be related to sperm morphology, motility or percentage of motility.

5. A method is proposed for utilizing bull hyaluronidase in the treatment of sterility. The enzyme is added directly to the semen specimen and then utilized for artificial insemination, or is packed into the cervix and followed by normal coitus. Six cases so treated are described in some detail.

6. The concentration of sperm and hyaluronidase about the tubal ovum is discussed. From a theoretical viewpoint the hyaluronidase content of 20 million sperm is necessary for follicle dispersal. This is in accord with the high concentration of sperm present in the normal ejaculate, and the amount considered clinically as sufficient to be considered fertile.

7. An attempt to demonstrate antibodies (or inhibitors) against bull hyaluronidase in the blood serum of sterile women was not successful.

We are indebted to Dr. Karl Meyer for his many fruitful suggestions and his kind interest in this work. The bull testis hyaluronidase preparation was provided through the courtesy of Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J. The authors wish to

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Pneumonia^{*}

Etiology, Diagnosis and Specific Treatment

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PNEUMONIA can no longer be considered as a single disease entity, but rather we must think of it as a group of specific infectious diseases caused by a variety of pathogenic agents each of which produces an acute febrile illness associated with an inflammatory reaction in the lungs. From the point of view of curative therapy, this concept became important first when type specific antipneumococcus serums were developed, since each serum was useful only against the pneumonia which was caused by the particular type of pneumococcus against which that serum was prepared. The sulfonamides are equally effective against all the pneumococcus types and when these drugs appeared, they essentially replaced specific serums in the treatment of all the pneumococcal pneumonias except in occasional resistant cases. In such cases type specific serums were still helpful.

The sulfonamides have proved effective also in the hemolytic streptococcic pneumonias but even the most effective sulfonamide drugs, namely, sulfathiazole and sulfadiazine, are only moderately effective in staphylococcic pneumonia and even less so in the pneumonias caused by Friedländer's bacillus or by influenza bacillus. Recently, in several parts of the United States there have appeared increasing numbers of cases of hemolytic streptococcic infections, including severe cases of pneumonia,

which failed to respond to adequate sulfonamide therapy clinically and which were proved by laboratory tests to be caused by organisms that are resistant to sulfonamides. The situation with respect to the hemolytic streptococcus may be analagous to that which has been universally recognized in gonococcic infections in which the widespread use of sulfonamide therapy has resulted in a steadily increasing proportion of sulfonamide-resistant strains.

Fortunately, penicillin made its appearance in the United States at about the same time. This antibiotic is effective against all types of pneumococci and also against all serological types of group A hemolytic streptococci which include all of the beta hemolytic streptococci that cause pneumonia. In addition, it is the most effective agent available against the pathogenic strains of *Staphylococcus aureus* and against the alpha hemolytic streptococci which may be responsible for occasional pneumonias. Even penicillin is not effective against the gram-negative bacilli including the *Hemophilus influenzae* (Pfeiffer's bacillus) and the *Klebsiella pneumoniae* (Friedländer's bacillus). Streptomycin, which has been used only in very limited clinical and laboratory tests, may prove effective against many of the strains of gram-negative bacilli. None of the known chemotherapeutic or antibiotic agents are effective against the pneumonias

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which are due to virus or rickettsial agents, nor are they effective in the pneumonias of unknown cause which are thought to be of virus etiology.

During the epidemic of influenza A which occurred in 1940 and 1941 an unusually large number of cases of *Staphylococcus aureus* pneumonia were recognized which occurred mainly as a complication of the influenza. Before that time, the staphylococcus had been recognized as a not infrequent cause of severe pneumonia and laryngotracheobronchitis in infants and young children, and occasionally as the cause of pneumonias complicating other staphylococcal infections (by hematogenous spread). In certain localities, it was the cause of the severe post-influenzal pneumonias during the pandemic of 1918. Since 1941, these staphylococcal pneumonias have been recognized in adults quite frequently in many clinics mostly, but not exclusively, as complications of influenza-like infections. During the 1940 and 1941 outbreak of influenza, it was shown that sulfadiazine and sulfathiazole were effective in varying degrees against these infections. Only in occasional early cases of staphylococcal pneumonia, however, were dramatic results observed in the treatment with these sulfonamides comparable to the responses which regularly follow the use of these same drugs in pneumococcal and streptococcal pneumonias. Penicillin has proved to be far more effective than any other chemotherapeutic or antibiotic now available in the treatment of these staphylococcal infections.

It is thus clear that pneumonia is due to a variety of living agents, bacterial or non-bacterial, and that the best results in each of these kinds of pneumonia will depend upon the choice and proper use of the effective therapeutic agent. What then are the most important etiological agents that cause pneumonia? How can they be recognized and diagnosed? Which effective drugs

and antibiotics are available to combat these specific infections and how are they best used?

Etiological Agents. The pathogenic agents which may cause pneumonia include various kinds of bacteria, fungi, rickettsias and viruses. In addition, there have been observed in recent years many cases of pneumonia having the characteristics of virus infections, but in which the etiological agent has not been isolated and proved conclusively. The relative incidence of these different forms of pneumonia varies widely in different countries, in different years and sometimes in different localities in the same country. Some of the salient differential features of the more common among the bacterial pneumonias and of most of the viral pneumonias are given in the accompanying table. The indications for the use of sulfonamides and antibiotics are given in each instance together with the optimum dosage. A few additional comments concerning these pneumonias and some of those not listed may be of interest.

Pneumococcal Pneumonia. This form has been declining steadily in frequency in the United States during the last decade except in a few localities. It probably still constitutes the largest proportion of the severe cases of pneumonia throughout the world. It is the easiest to recognize because of the characteristic history, sputum and later the signs of frank consolidation. In these cases, improvement in the acute symptoms, in toxemia and dyspnea often occurs within twelve hours and usually within twenty-four to forty-eight hours after treatment with sulfonamides or penicillin in adequate doses is started. The mortality has been reduced by this treatment from about 30 per cent to less than 10 per cent and the fatalities are limited chiefly to persons over fifty years old, those with severe underlying conditions and patients in whom treatment has been delayed too long.

Pneumonia—Finland

DISTINCTIVE FEATURES AND SPECIFIC TREATMENT OF THE COMMON FORMS OF PNEUMONIA

Clinical and Laboratory Features	Causative Agent					Viruses (Known or Probable)
	Pneumococcus	Hemolytic Streptococcus	Staphylococcus Aureus	Friedländer's Bacillus	Influenza Bacillus	
Occurrence.....	After common cold or bronchitis	After streptococcal infections (tonsillitis, scarlet fever), measles or influenza	Infancy; early childhood; adults after influenza; or metastatic from other foci	Old persons or those with chronic respiratory infections; alcoholics; complicating urinary or intestinal infections	Infancy; early childhood; adults with chronic bronchopulmonary infections; after influenza virus infections	Predominantly adolescents and young adults. Vary with virus e.g., psittacosis and ornithosis (after exposure to sick birds)
History and Symptoms.....	Sudden onset; shaking chill; localized pleuritic pain	Sudden or gradual; chills or chilly sensations; presternal pain (occasional pleurisy); hoarseness, dyspnea	Sudden or gradual; chills or chilly sensations; dyspnea and presternal pain during or after influenza	Chronic cough; onset with chills, pleurisy and dyspnea; rapid progression	Acute; rapidly progressing; severe prostration, dyspnea, and cyanosis, especially after clinical influenza	Gradual onset, headache, chilly sensations (chill uncommon), dry cough, presternal soreness (pleurisy uncommon)
Physical Findings.	Suppressed breath sounds and occasional râles early; then lobar consolidation; short grunting respiration	Red throat with exudate; musical and crepitant râles; scattered consolidation; signs of pleural fluid early	Diffuse râles and patchy consolidations; relatively slow pulse in post-influenzal cases	Patchy or confluent bronchopneumonia; very rapid respirations; marked cyanosis; upper lobes frequently involved	Laryngotracheobronchitis in infants; patchy and confluent consolidation	Crackling râles, scattered or migratory; dyspnea and cyanosis on light exertion; anis on light exertion; patchy atelectasis or consolidation later
Sputum.....	Rust-colored; gram-positive lancet-shaped, encapsulated diplococci predominant in smears	Blood-streaked or bloody; chains of cocci in smears	Purulent, chalky or mixed with varying amounts of blood (pink to brick red); clumps of cocci in smears	Bloody, mucoid, stringy; numerous stubby gram-negative bacilli with large capsules in smears	Bloody or blood tinged, mucopurulent with pleomorphic short slender negative bacilli in smears	Scant at first; yellowish, mucoid (rarely blood tinged), purulent later, few organisms in smears
X-ray.....	Uniform density, lobar distribution	Diffuse patchy densities; pleural fluid early	Peribronchial patchy or nodular densities; confluent with abscesses later	Diffuse patchy densities early; confluent dense consolidation (like fluid) upper lobes frequently involved	Diffuse patchy or military densities	Soft nodular (miliary) densities; may spread from hilar areas of consolidation or atelectasis later
White Blood Count.....	15,000-20,000; mostly polyps; (leukopenia in severest cases)	15,000-30,000; mostly polyps with toxic granules	Variable; leukopenia early in post-influenzal cases; elevated later	Leukopenia (2,000-6,000) frequent; toxic polyps predominant; elevated later	Leukopenia early	Normal or low; slightly elevated later; increases in monocytes
Sulfonamide or Antibiotic Therapy.....	Sulfadiazine, 4 Gm. then 1 Gm. every 4 hours or penicillin 15,000 or 20,000 units every 2 or 3 hours for 24 hours; then 15,000 every 3 hours; stop after 2 or 3 days of normal temperature and subsidence of acute symptoms	Same as for pneumococcus except continue for 5 to 7 days after temperature is normal	Penicillin 20,000 or 25,000 units every 2 or 3 hours depending on severity until temperature reaches normal and acute symptoms subside. Continue 20,000 units every 3 hours for 7 to 14 days longer. Sulfadiazine or sulfathiazole in full doses may be used as a supplement	Sulfadiazine as under pneumococcus; intravenous or subcutaneous injection of 5 Gm. of sodium sulfadiazine may be used for initial dose. Penicillin by inhalation, 50,000 units every 3 or 4 hours may be used. Streptomycin intramuscular or by inhalation when available	Same as for Friedländer's	Sulfonamides and antibiotics not usually effective except when there is complicating bacterial infection as evidenced by purulent sputum with many organisms, leukocytosis, change in clinical course or physical findings, then use in full dose as for bacterial pneumonias
Commonest Complication and Its Management...	Empyema, usually after first week; thoracentesis and intrapleural injections of penicillin, 50,000 units in 50 to 200 cc. of saline. Repeat at 1 to 3-day intervals so long as purulent or infected fluid forms; surgery after 2 to 3 weeks if indicated	Empyema may develop during first 3 or 4 days; large amounts of serousanguinous, then fibrinopurulent fluid; treatment same as for pneumococcus empyema; surgery only if thick pus or thick-walled cavity persists	Multiple pulmonary abscesses; no additional treatment indicated early; surgery for drainage may be necessary for large abscess which fails to heal. Penicillin by inhalation, 25,000-50,000 units every 3 or 4 hours may be tried first; empyema or pyopneumothorax treat as under pneumococcus	Multiple lung abscesses, may resemble pulmonary tuberculosis with cavitation. Streptomycin by inhalation when available (dosage 20,000-30,000 units every 3 or 4 hours). Recurrence frequent in recurrent cases	Obstruction in infants may require intubation or tracheotomy; hemoptysis, pulmonary abscesses or bronchiectasis, especially in post-influenzal cases. Streptomycin by inhalation may prove helpful	Complications infrequent; convalescence may be prolonged with weakness and persistent cough for several weeks

Purulent complications are infrequent if treatment is undertaken early. Furthermore, empyema, the commonest of these complications, will usually yield to treatment by aspiration of the empyema fluid and instillation of penicillin. If the exudate is very thick, irrigation with saline to remove some of this exudate before instilling the penicillin may help bring about early recovery and avoid open surgical drainage in most cases. Systemic treatment with penicillin or sulfonamides may be continued until the patient remains completely afebrile for several days. The aspirations and the local instillations of penicillin may be discontinued if the fluid remains free of organisms and the patient shows no further signs of active infection, unless it continues to accumulate in appreciable amounts, in which case, the aspirations and penicillin should be continued.

Streptococcic Pneumonia. This is a severe and often rapidly advancing form of pneumonia which usually begins with a pharyngitis followed by laryngitis and tracheitis. The mortality in this form of pneumonia is often as high as 40 per cent and young adults are frequently attacked. In many cases, particularly in epidemic forms of the disease which occur during outbreaks of measles, scarlet fever or influenza, there is a rapid accumulation of thin serosanguineous fluid during the first three or four days of the disease while the pulmonary infection is still progressing. This results in a marked increase in dyspnea and toxemia which is often dramatically improved by simple aspiration of the fluid. Nowadays, the administration of sulfonamides and particularly of penicillin may delay or prevent the appearance of this form of empyema and instillation of penicillin into the pleural cavity after aspiration of the fluid may prevent the reappearance of the toxemia and in many instances, bring about a rapid and complete cure without re-accumulation of this fluid. Continued treatment with sulfonamides

alone after the fluid becomes thick and purulent may sometimes result in a rigid and thick-walled empyema cavity which may become difficult to obliterate surgically. This can probably be avoided by early evacuation of fluid and penicillin instillations, the latter preceded by saline irrigations if the fluid is thick and fibrinopurulent.

Because of the tendency of this form of pneumonia to be accompanied by abscess formation and other purulent complications, it is best to continue with sulfonamide or penicillin treatment somewhat longer than in cases of pneumococcic pneumonia. Treatment for five to seven days after the temperature has become normal is probably adequate in most cases. The exact mortality in streptococcic pneumonia when properly treated with sulfonamides and penicillin is not known, but it should not be much greater than in the pneumococcic pneumonias.

Most of the streptococcic pneumonias are caused by strains of group A beta hemolytic streptococci and some of these may be resistant to sulfonamide drugs but all are susceptible to penicillin. Occasionally, a similar type of infection is encountered in which the sputum and pleural exudate and sometimes the blood culture yield *Streptococcus viridans* in pure culture. In such cases, the sulfonamide drugs are of no help and it is necessary to resort entirely to penicillin. The results of penicillin treatment in such cases are usually highly satisfactory.

Staphylococcic Pneumonia. This is a form of pneumonia which has always been important in pediatric practice, but it has become increasingly important in adults in recent years. There is a fulminating acute variety which occurs during or after an attack of influenza and which may prove fatal within the first three or four days or even within a few hours of the time when the symptoms or signs of pulmonary involve-

ment are first recognized. Other cases vary all the way from this form to a subacute and chronic fibrosing type of diffuse pneumonia associated with multiple abscess formation and pyothorax. The mortality in staphylococcic pneumonia was usually about 50 per cent and almost all of the fulminating cases proved fatal. With early and adequate sulfonamide and penicillin therapy, some of the patients with apparently fulminating cases have recovered and the mortality and disability among the others has been markedly reduced.

Anatomically, the fulminating type of case is associated with a severe laryngotracheobronchitis and a diffuse hemorrhagic confluent lobular bronchopneumonia. In many areas, usually around the bronchi or bronchioles, there is evidence of necrosis of the alveoli and masses of cocci can be seen in such areas. In the less acute cases, there are numerous peribronchial abscesses which are small at first and later may become confluent and either break into the bronchi or into the pleural cavity. The replacement of some of these abscesses by fibrous tissue results in a chronic type of pneumonia with increasing difficulties in respiration and sometimes death from cor pulmonale. During the first few days of the disease many of the mild or moderately severe cases may be difficult to distinguish by their physical signs and x-ray findings and even by their symptoms from cases of primary viral pneumonia. This is particularly true if the white blood cell count is normal or low as is sometimes the case in the early and acute phase of both diseases. The sputum is purulent and often mixed with blood. Smears show many staphylococci which on culture prove to be hemolytic and coagulase positive. The character of the sputum should, therefore, help to differentiate the staphylococcic from the viral pneumonias.

Because of the fact that the staphylococci are much less susceptible to sulfonamides

and penicillin than are the pneumococci and streptococci, treatment must be more intensive. If sulfonamide drugs are used, they must be given in larger doses. Usually 8 to 10 Gm. a day are necessary in adults, and it is necessary to give greater amounts of fluid in order to avoid renal complications. When it is possible to obtain blood chemical determination, it is advisable to keep the blood level of sulfadiazine between 10 and 15 mg. per 100 cc. of blood and sulfathiazole between 8 and 10 mg. per 100 cc. (Levels of 7 to 10 mg. per cent of sulfadiazine or 4 to 6 mg. per cent of sulfathiazole are usually adequate in pneumococcic pneumonias.) Since prolonged treatment is indicated, it may be necessary to use these two drugs in succession if drug fever or rash occurs after a week or so of treatment with one of them. The minimum dose of penicillin that should be used in staphylococcal pneumonias is 20,000 units every three hours and larger amounts up to 25,000 units every two hours may be needed early in the severe cases. Furthermore, because of the tendency to form multiple abscesses, the treatment must be prolonged for one to two weeks after the acute symptoms have subsided. This is necessary in order to assure the healing or the evacuation of these abscesses before the antibiotic therapy is stopped. Because of the severe laryngotracheobronchitis that is common in these cases and because the abscesses tend to be peribronchial in location, treatment by inhalation of nebulized penicillin in a manner suggested by Barach may prove helpful and result in more rapid healing. At the present time, it is not possible to say whether sulfonamides are of sufficient additional benefit in penicillin treated patients to warrant the added risks and additional precautions required for their prolonged use in the large doses that are needed.

Friedländer's Pneumonia. This is a relatively infrequent, but very severe variety in

which the mortality in acute cases may be as high as 70 to 80 per cent. There are instances of epidemics of this disease recorded in Germany; one in a children's home and the other in a prison camp, and in these outbreaks the mortality was not so high. Intensive sulfadiazine therapy used in the same manner as in severe staphylococcic infections has resulted in reduction in the mortality to about 50 per cent. Occasional cases are reported in which large doses of penicillin have apparently resulted in recovery. Such cases are probably due to strains of Friedländer bacillus which are relatively susceptible to this antibiotic. More recently, streptomycin has been used with considerable success in a very small number of cases in the United States. In this disease, too, there is considerable necrosis of pulmonary tissue resulting probably from ischemia caused by obstruction with the thick gelatinous exudate. Prolonged therapy for one to two weeks after essential recovery is therefore indicated. Inhalation of nebulized antibiotics may prove useful especially after the acute phase when abscess formation begins to take place.

Pfeiffer Bacillus Pneumonia. This form was widely prevalent during the pandemic of 1918, and probably before that in 1890. Clinically and pathologically the disease is similar to the fulminating acute forms of hemolytic staphylococcus aureus pneumonia, but less acute forms probably also occur. The mortality in these pneumonias is also quite high. The extreme toxemia and necrosis of tissues that occurs is thought to be due in part at least to the toxic product of the influenza bacillus. The underlying causative agent of pandemic influenza which is presumably a virus, probably also plays an important part in the pathogenesis of these changes. The influenza bacillus may also cause acute laryngotracheobronchitis in infants and young children and occasionally is the cause

of pneumonia in adults as a complication of chronic bronchitis or bronchiectasis in which these organisms are frequently found.

The indications for specific treatment are essentially the same as in the Friedländer bacillus infections. The main reliance at present is on intensive sulfonamide therapy with sulfadiazine or sulfathiazole. Occasional strains of influenza bacillus are slightly susceptible to penicillin and when such strains are involved, the use of large parenteral doses of that agent or treatment by inhalation may be effective. Judging from the results in influenza bacillus meningitis, streptomycin may prove to be the most effective agent against these organisms, but there is considerable strain variation in the susceptibility of influenza bacilli to streptomycin. There are as yet no clinical results reported to substantiate the value of streptomycin in influenza bacillus pneumonia.

Other Bacterial Pneumonias. There are rare cases of pneumonia due to other cocci such as *Micrococcus tetragenous*, *meningococcus*, or *Micrococcus catarrhalis* and others caused by bacilli such as those of anthrax, plague and tularemia. These pneumonias may be primary or they may be secondary to systemic or other focal infections with the same organisms. The meningococcal infections respond best to sulfonamide therapy while the other coccal and gram-positive bacillary infections should yield to penicillin, alone or combined with sulfonamides. There is evidence that tularemia is highly susceptible to streptomycin and the pneumonic form will probably also respond to this agent. The same may prove to be true of the pneumonic forms of plague.

Pneumonias Caused by Fungi. Certain fungus infections, namely, moniliasis and coccidiomycosis may occur in acute bronchopulmonary forms. *Candida albicans* is the organism commonly found in bronchopulmonary moniliasis which is said to occur mostly among tea tasters and in persons who

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handle grains. The organism, however, is not infrequently found in the mouth of normal individuals and under unusual conditions may give rise to lower respiratory tract infections. It is of interest that the first case of infection with *Coccidioides immitis* was reported from Argentina, but the total number of authentic cases from South America is very few. The organism is very prevalent among wild rodents in certain parts of western and southwestern United States and most of the human cases of coccidioidomycosis have been recognized in those regions. These bronchopulmonary mycoses are usually subacute or chronic in nature and associated with multiple abscess formation giving a picture which closely simulates pulmonary tuberculosis. Some of the acute forms are not unlike atypical pneumonias of other kinds, particularly early in their course. The characteristic forms of monilia in the sputum are oval, thin-walled, yeast-like cells, 2 to 4 millimicra in size and occasionally mycelial elements and budding forms are found. The sputum usually has a distinct yeasty odor. *Coccidioides* may appear in sputum as spherical, thin-walled structures, 20 to 80 millimicra in diameter and filled with small round endospores which may eventually be freed by rupture of the cell wall. It is important to recognize these forms of pneumonia early because they are likely to become chronic and then may be confused with pulmonary tuberculosis. There is no effective therapy although iodides are usually used and sometimes seem to be somewhat effective.

Rickettsial Pneumonias. A diffuse patchy type of pneumonia has frequently been observed in the course of severe rickettsial infections such as typhus, Rocky Mountain spotted fever and South African tick-bite fever. Although secondary bacterial infections may play a rôle in some of these pneumonias, autopsies in fatal cases have

revealed an interstitial type of infiltration in the lungs with mononuclear cells of a type suggestive of rickettsial rather than bacterial infection. Similar pulmonary lesions are easily induced in experimental animals by intranasal infection with rickettsias.

A new form of rickettsial infection called Q fever has been recognized in Australia since 1933. This disease which attacks mostly slaughter house workers and foresters gives a picture like that of severe influenza, but there is an associated "typhoid state" with severe drowsiness and even stupor. The causative agent can be obtained from blood or urine of patients by injection of guinea pigs or mice. After an incubation period of eight to fourteen days, large intracytoplasmic colonies of the rickettsias are seen in impression smears of the spleens of these animals. Specific antibodies to the rickettsias develop in the patients, but agglutinins for proteus X19 or XK do not develop. A similar if not identical rickettsial agent has been found in ticks in the western United States, and sporadic cases of so-called American Q fever have occurred in this region. Laboratory infections, both clinical and latent, have been recognized in Australia and in this country. At least two outbreaks of laboratory infections in this country have been associated with severe atypical pneumonia, which clinically and by x-ray were very similar to other atypical pneumonias of unknown etiology, the so-called viral pneumonias. Recently, outbreaks of severe pneumonia due to the same or to a very similar agent have been recognized in the Mediterranean area and cases from this source have apparently been transferred to the United States in military units. No specific treatment is now known for any of these rickettsial infections.

Pneumonia Caused by Known Viruses. Certain virus diseases are accompanied in occasional severe cases by pulmonary lesions presumably due to the same agent. Similar

lesions are readily produced in experimental animals by intranasal inoculation of many viruses. Human cases of severe pneumonia due to the virus of lymphocytic choriomeningitis have been described recently and respiratory symptoms have occurred in laboratory workers accidentally infected by inhalation of the virus of lymphogranuloma venereum. Pneumonia complicating measles or smallpox may also be due to these respective viruses although the majority of such pneumonias are probably secondary bacterial infections. Cases of pneumonia apparently acquired from exposure to sick kittens have recently been observed. A virus capable of producing transmissible pulmonary lesions in kittens has also been described, but the relation of this virus to human cases has not been established. The commonest viruses which specifically attack the respiratory tract and produce pneumonia are those of influenza and the psittacosis group of viruses.

Influenza Virus Pneumonia. It is well recognized that in many severe cases of clinical influenza there are symptoms, physical signs and x-ray findings suggesting involvement of the trachea, bronchi and lungs. Scattered musical and crepitant râles and fine mottled infiltration seen in x-ray in the lungs are all that can be made out, but there is usually a severe cough and often bloody sputum. In the extensive pneumonias which occur as a complication of influenza, secondary bacterial infections frequently play a dominant rôle and probably determine the pathological character and the severity of the pulmonary infections in most instances. Some cases, however, have been described in which evidence of bacterial infection could not be demonstrated after careful cultural and histological study of the pulmonary lesions and the pneumonia in those cases most likely is due to infection with influenza virus. An analogous situation is found in experimental in-

fluenza virus infections. In certain animals, notably mice and ferrets, the influenza virus alone produces extensive and fatal pulmonary lesions in the absence of bacteria. In swine, however, the influenza virus alone produces only a mild infection with involvement limited to the upper respiratory tract simulating ordinary cases of human clinical influenza. A combination of the virus with influenza bacillus produces an extensive pneumonia which is highly fatal to swine but the bacillus itself does not produce pulmonary lesions in the absence of a virus. The situation in the swine may, therefore, be analogous to that found in the severe pneumonias observed in the pandemic of 1918 in which influenza bacillus was found in pure culture. The recent demonstration of a soluble toxin in influenza A virus may help to explain some of the severe hemorrhagic lesions which result in uncomplicated virus infection.

There is no known specific treatment of influenza virus infections. Cases in which secondary bacterial infection is present should be treated vigorously for that particular bacterial infection. The evidence that beneficial effects can be obtained from influenza antiserums or from convalescent serums is inconclusive. Favorable results have been obtained recently in the prevention of infections with the viruses of influenza A and B by inoculation of vaccine containing these viruses. The vaccine must be given from ten days to a few months in advance of exposure.

Psittacosis, Ornithosis and Related Infections. Psittacosis has been recognized since 1880 as a severe disease acquired from sick parrots and clinically resembles influenza on the one hand, and typhoid on the other. The chief pathological finding is an atypical pneumonia. The virus etiology of this disease was established during the pandemic of 1929 and 1930 which arose from an epizootic among Brazilian parrots and was first re-

ported from Buenos Aires. The causative agent has been found in many species of exotic birds and related viruses are widespread among pigeons and many other species of wild and domestic fowl. Infections acquired from the latter viruses are called "ornithosis" as suggested by Meyer. Other serologically related filtrable viruses are found in normal laboratory animals and are capable of producing pulmonary lesions in those animals, and these serve to confuse the results of inoculations with human materials. In addition, still other viruses which are responsible for such entirely different diseases as lymphogranuloma venereum, inclusion conjunctivitis and trachoma are immunologically closely related to the viruses of psittacosis and ornithosis and offer another source of confusion in serological tests.

Clinically, the only features which distinguish psittacosis and ornithosis from other primary non-bacterial pneumonias is the severity of the course and the "typhoid picture." The diagnosis is suspected by the history of exposure to sick birds and may be established by inoculation of sputum or material aspirated from the lungs into mice or guinea pigs and then demonstrating the characteristic coccobacillary inclusions in impression smears of the spleen. The different species of viruses vary in their pathogenicity for different animals and in the susceptibility of animals to inoculation by different routes.

Because of the widespread occurrence of these viruses among many common varieties of birds, ornithosis was thought to be the cause of the widely prevalent cases of so-called virus pneumonia. Extensive attempts to obtain these viruses in such cases and to prove their etiological relationship by serological studies have not borne out this suspicion. The proved human cases have been limited almost entirely to persons intimately exposed to sick birds. A small outbreak of

severe pneumonitis with a high mortality has recently been described in Louisiana and a new virus of this same group was proved to be the causative agent in these cases. Still another related virus was isolated from two fatal cases in Illinois.

Although the viruses of lymphogranuloma venereum, inclusion conjunctivitis and trachoma are susceptible to sulfonamides, these drugs have little or no effect on psittacosis or ornithosis. Occasional strains may prove to be susceptible to penicillin or to other antibiotics especially if they are given early and in comparatively large doses. Secondary bacterial infections are not uncommon in these cases and may greatly increase the severity of these pneumonias. In that event, the appropriate antibacterial agent given in full doses may bring about considerable improvement.

Primary Pneumonia of Unknown Etiology—
"Virus Pneumonia." This form of pneumonia has been recognized during the past few years in military establishments, schools, colleges and among hospital personnel, especially doctors, nurses and attendants. It is now being recognized with increasing frequency in general civilian and hospital practice, although the diagnosis is undoubtedly being made much more often than is warranted. The cases have been variously referred to as "influenza pneumonia," atypical bronchopneumonia, disseminated focal pneumonia, acute pneumonitis, and by many other designations. The official terminology adopted for classification purposes by the United States Army was "primary atypical pneumonia, etiology unknown," but the disease is generally referred to by the name originally suggested by Reimann, namely, "virus pneumonia." The same writer has more recently suggested the term "viroid." Outbreaks of this disease have been described in isolated camps, schools and institutions prior to 1940, but it assumed epidemic proportions in the United

States and Great Britain during 1942 and 1943.

The clinical features of this disease are quite similar to those of other pneumonias caused by known viruses or rickettsias and are listed in the table. In this disease, however, there are widespread variations in the severity of the symptoms and in the extent of the pulmonary lesion. The majority of cases in adolescents and young adults are mild and may involve only a portion of one or both lungs extending out slightly from the hilum. Others involve most or all of both lungs and may give a picture which on physical examination and by *x*-ray closely resembles that of acute miliary tuberculosis. Cases of the latter type may be extremely severe and may have marked dyspnea and cyanosis. Headache may be a prominent feature in the majority of cases, even the mild ones. Cough is often very irritating and unproductive for several days. Both of these symptoms may be difficult to control with the usual remedies. The fever may be irregular or sustained but usually is not higher than 103°F. It may continue for anywhere from three to twenty-one days or even longer, but in the majority of cases the febrile course lasts from seven to fourteen days. Pleurisy and complications other than prolonged cough and asthenia are uncommon.

The blood in many cases, especially the severe ones, may develop cold agglutinins; that is, the serum or plasma develops the property of agglutinating human red blood cells irrespective of the blood group and including the patients own cells when exposed to the cold. These cold agglutinins first appear during the middle of the second week of the disease, reach a maximum titer within a few days and may then decline or disappear quite rapidly. If the titer of cold agglutinins in the blood is very high, agglutination of the red blood cells may take

place at room temperature and may be recognized by the difficulty in making blood counts due to the clumping of the red blood cells. Significant titers of cold agglutinins rarely develop in the course of other acute respiratory infections or in other virus diseases and may, therefore, serve as an aid in the differential diagnosis. Workers at the Rockefeller Institute have isolated a capsulated strain of indifferent streptococcus and demonstrated the development of agglutinins for this streptococcus in convalescent serums from these cases.

Many attempts have been made to isolate the causative virus from cases of this sort. As already intimated, known viruses or rickettsial agents including those of psittacosis, ornithosis and *Q* fever account for a negligible proportion of these cases. That a filtrable agent is the cause, at least of some characteristic cases of this disease, has been demonstrated by a carefully controlled experiment in humans carried out by the Commission on Acute Respiratory Diseases of the United States Army. Human volunteers inhaled filtered sputum from typical cases and developed identical clinical symptoms and physical and *x*-ray signs as were found in the cases from which the sputum was obtained. Boiled sputum failed to reproduce the disease. A rise in cold agglutinins occurred in the experimentally induced cases. Many attempts by the same workers to transmit the disease to experimental animals by similar material from comparable cases have failed. Several other groups of workers, however, have isolated filtrable agents and produced lesions in animals with materials from human cases. Eaton and his co-workers in California isolated a virus which they were able to propagate in fertile hen's eggs and which was neutralized by the convalescent serum of a number of characteristic cases of this disease, but not by the serums of cases from other diseases. None

of these findings have been adequately confirmed.

There is no specific treatment in this form of pneumonia. Sulfonamide drugs and penicillin are indicated when there is any reason to suspect secondary bacterial invasion by the change in the character of fever, the occurrence of leukocytosis or purulent sputum and particularly by the demonstra-

tion of bacteria in large numbers in the sputum.

When used, these agents should be given in full doses as indicated by the type of predominant organism seen in the smears or obtained in cultures. The mortality in these cases is low, but there may be a long period of asthenia with persistent cough after the febrile course in many cases.

Curare*

A Review of Its Therapeutic Effects and Their Physiological Basis

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THE clinical use of curare is based on its ability to create a transient block to neuromuscular transmission. This phenomenon was first described by Claude Bernard,¹ who demonstrated that the site of action of the drug was at some point between the nerve fiber and the muscle.

Historical Background. It was tribal custom in widespread areas of South America to prepare arrow poisons from plants indigenous to the local region. Collectively these crude extracts were known as curare. As prepared, they contained various alkaloid fractions in differing proportions. These alkaloids often had many pharmacologic effects other than those described by Bernard in his experiments. The samples reaching civilization naturally varied widely in origin and alkaloid content.²

Since the source of supply was so equivocal and the active agent poorly understood, curare until recently remained an unpredictable therapeutic tool. Nevertheless, it is surprising with what speed the properties of the drug were exploited. Jousset,³ Benedikt⁴ and others used curare clinically almost as soon as Bernard's experiments were complete. Due to the lack of a reliable preparation rather than to a paucity of interest, clinical experimentation remained dormant for many years. The literature of the period, however, is of intense historical interest.

In recent years, important steps were

taken by King,⁵ and by Wintersteiner and Dutcher,⁶ in isolating and identifying a pure crystalline tubocurarine from the vast number of specimens available. Knowledge of the alkaloid previously was confused both as to its exact botanical origin and pharmacologic properties. With this clarification, it was possible to investigate a drug of predictable properties and toxicity. The determination of its exact mode of action at the myoneural junction, however, is still incompletely realized.

Tubocurarine is now known to be a quaternary ammonium salt. Such salts, in general, have the property of paralyzing conduction at the myoneural junction.⁷ Among the group, however, tubocurarine is the only alkaloid which, in certain definite concentrations, has an almost pure myoneural junction effect. This property, of great clinical significance, is most probably related to the configuration of the molecule as well as to chemical composition. Acetylcholine and prostigmin have a similar configuration and under certain circumstances can be made to cause or degenerate a muscle twitch.⁸ Molecules of this stereochemical type exert specific effects on vital membrane structure. Further study of these membrane phenomena will add to our knowledge of the physiological action of quaternary ammonium salts and the mechanism of neuromuscular conduction.

Recent physiological data^{9,10,11,12,13} make

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the following hypothesis a probable one. The myoneural junction is an excitable membrane. A transmitter substance, whether it be acetyl choline or local action currents, induces a potential by actively depolarizing the junctional region. Normally, this depolarization reaches a critical value and produces the muscle spike by spreading electrotonically and depolarizing the neighboring area. In fully curarized muscle, this so-called end plate potential rises to a subthreshold level and then decays without initiating a muscle response. If curare merely paralyzed skeletal muscle in this manner, it would have limited clinical value other than in therapy requiring a paralyzant effect. Actually, the size of the end plate potential depends, to some extent, on the concentration of drug. Therefore, the degree of block can be controlled. Frequencies outside a critical range, or abnormally sustained, can be blocked while those of different characteristics will still evoke a normal muscle twitch. Since the normal excitatory state at the junctional membrane depends on rapid reversibility of polarization, any mechanism which either reduces this capacity or maintains the membrane in a single phase for abnormal periods of time acts as a depressant. Such a process may explain why in certain concentrations acetyl choline and prostigmin are depressants of neuromuscular conduction.

These observations underlie the present-day concept of curare therapy. We do not always attempt to paralyze the myoneural junction, but sometimes desire to create a block to certain frequencies imposed on the myoneural junction by the disease process. It is thus perfectly feasible to obtain a therapeutic effect without loss of voluntary power.

CLINICAL APPLICATIONS

From the foregoing, it becomes obvious that the clinical use of curare depends upon

maintaining varying degrees of block to neuromuscular conduction. On this basis a sharp division may be made amongst its various applications:

- I. *Where total or subtotal block is necessary* (paralyzant effect)
 - A. Surgical anesthesia
 - B. Shock therapy
 - C. Amelioration of convulsions, as in tetanus
- II. *Where partial block is desired* (lissive effect)
 - A. Muscle spasm
 1. As in actual trauma to muscle, myositis
 2. Reflex spasm, in orthopedic disturbances, low back syndrome, etc.
 3. With arthritis, acute
 - B. Spasticity
 1. Spinal cord injury
 2. Birth injury
 3. Degenerative diseases of the CNS
 - C. Rigidity
 1. Paralysis agitans
 - D. Dystonia and athetosis
 - E. States resembling spasm and spasticity as in poliomyelitis

IA. USE OF CURARE IN SURGICAL ANESTHESIA

In 1930, Dr. de Caux,* in England, experimented unsuccessfully with the use of curare combined with nitrous oxide in surgical anesthesia. His failure was undoubtedly due to the crude preparation then available. Griffith,¹⁴ of Montreal, in 1942, published for the first time a description of the clinical use of curare as an adjuvant to anesthesia. His original work was done at the suggestion of Dr. L. A. Wright of New York. Many papers have since defined the useful technics, among them admirable contributions from the original observers.

The preparation in use today is an aque-

* Personal communication.

ous solution containing 20 mg. or units of standard curare per cc. It is titrated for potency by the head drop test in rabbits, which gives an excellent end point. It is apparently a stable and predictable agent.

Clinical experimentation has brought out the need for adequate premedication.¹⁵ Drugs of the hyoscyamus series are useful in preventing excessive salivation and mucus. It should be borne in mind that the dangers of aspiration are heightened by curare, which depresses the pharyngeal reflexes.¹⁶ Intubation is indicated whenever aspiration or regurgitation is a problem.

Choice of Anesthetic. Every anesthetic has well defined properties which govern its occasional choice. The ability of curare to add specific degrees of muscle relaxation¹⁷ to all forms of anesthesia has increased the usefulness of some agents which would otherwise be severely limited in value. In addition, the anesthesia concentration need not be carried to the levels previously necessary, since relaxation can be effectively maintained without classical third-stage anesthesia. With good relaxation, trauma can be reduced and operating time cut down. Postoperative complications incident to prolonged anesthesia can likewise be reduced. Consciousness and normal reflexes can be returned much more rapidly because of the low concentrations of anesthetic needed.

A large body of evidence has been collected with regard to the usefulness of curare in combination with various anesthetic agents:

Cyclopropane¹⁸ has proven particularly good in combination with curare. The patient can be kept at a light level of anesthesia and the cardiac irregularities associated with high concentrations of cyclopropane avoided.

Ether: This drug is in itself capable of a curariform effect in clinical concentrations.¹⁹ The dosage of curare must, there-

fore, be significantly lessened to avoid overdosage. With lowered concentrations of ether, the nausea, vomiting and acidosis of the post-ether recovery period can be markedly lessened.

Sodium Pentothal: Use of pentothal with curare combines two respiratory depressants. However, with adequate control of respiratory exchange the risk is not great.^{20,21,22} The quantity of pentothal can be sharply cut down, and its poor relaxant qualities circumvented while its admirable qualities such as ease of administration can be fully utilized.

Ethylene and Nitrous Oxide:^{21,22,23} The special properties of these agents can be much more fully exploited when predictable relaxation is added.

Spinal Anesthesia: The results with curare compare favorably with those obtained in spinal anesthesia.¹⁹ Intrathecal therapy is avoided, and the unpleasant nausea and pulling sensation during spinal anesthesia eliminated. High abdominal surgery can be performed with general anesthetics with facility equal to the best results obtained under spinal anesthesia.

Method of Administration. The aqueous preparation contains 20 units of standard curare to the cc. Intravenous injection is used except rarely when intramuscular administration is employed. The latter is associated with a slower onset of desired effect and a more prolonged period of relaxation.

Dosage requirements vary. Among the factors involved are body weight, anesthetic agent, area of incision and type of disorder. The average dose is 5 cc. or 100 units, given over a period of ten seconds. The dosage is calculated from the foregoing criteria, and the individual experience and preference of the anesthetist. A clinical response is noted within two minutes if the drug is given intravenously and within fifteen minutes when given intramuscularly. Opinion is

divided as to the exact technic of administration. In certain clinics a large single initial dose is given. Elsewhere, divided injections are used, with drug added as indicated by the needs of the surgeon. Large doses given very rapidly may cause respiratory paralysis with a fall in blood pressure incident to the pooling of blood in the extremities. Where normal alveolar exchange is not rapidly facilitated, CO_2 may collect with a secondary abrupt rise in blood pressure.²⁴ This state responds rapidly to normal respiratory exchange.

Because of the rapid effect, the drug is usually injected a few moments before the peritoneum is opened. With average doses, the period of relaxation lasts approximately twenty-five minutes. During this period the surgeon has the advantage of good relaxation, even though the patient may be carried at unusually light levels of anesthesia.

When, for pertinent reasons or not, complete respiratory paralysis occurs, use of positive pressure to facilitate respiratory exchange will, if properly maintained, result in return of adequate spontaneous excursion within five minutes or less. Prostigmin may hasten this return, but is usually unnecessary. An adequate airway and good exchange are the best antidotes. It should be emphasized that the indication for curare therapy is the induction of motor relaxation during surgical procedures. Its use to lessen difficulties incident to poor induction or poor choice of anesthesia is to be decried.

Endoscopy. The technics of the use of curare to facilitate laryngoscopy, esophagoscopy and bronchoscopy are well documented and fully substantiated.²⁵ Bronchospasm as a complication of curare therapy has been reported and deserves further study.²⁶ However, experience seems to be that care in the rate of administration and choice of dosage will help to avoid this complication.

In summary, it can be stated that the anesthetist has for the first time a tool easy of handling, rarely toxic, capable of affording predictable relaxation during surgery. The opportunity to carry patients at light levels of anesthesia has contributed greatly to a reduction in operative and postoperative complication. Curare seems to be a permanent addition to the battery of anesthetic aids.

CLINICAL OBSERVATIONS DURING CURARIZATION

Curarization progresses in orderly fashion under normal circumstances. The small striated muscles are first affected. These include the stapedius and tensor tympani, the extra-ocular muscles of the eye and the small muscles of the toes. As the concentration rises, the last muscle to be involved is the diaphragm. Fortunately, from a clinical standpoint, relaxation of the abdominal muscles occurs well before the diaphragm is affected.

The patient first notes a fuzziness of vision, probably related to iris relaxation. Coincidence or careful testing will reveal increased aural sensitivity to low notes, based on a loss of the protective action of the tensor tympani and stapedius. A feeling of warmth and flushing in the extremities may be described. Double vision next appears. Many patients describe a headache in the frontal region, most often a circumscribed area on the left. Dizziness may be noted. Whether this subjective sensation is central or related to the visual changes and a slight drop in systolic pressure is not known.

These phenomena are followed by a feeling of pleasurable relaxation as the larger skeletal muscles are affected. At this point a drop of about 20 points in systolic pressure is recorded. Drowsiness may now supervene. About 10 per cent of patients consistently describe a feeling of euphoria

or "jag" during this stage. In others, a slightly higher level is accompanied by a feeling of tension and increased muscle awareness. As the concentration increases relaxation merges into paresis and paralysis of striated muscle. There is no true hypnotic or sedative effect but if the blood level is rapidly pushed further an abrupt loss of consciousness may occur, unrelated to adequate respiration.

All these effects rapidly disappear as curare is eliminated by the renal apparatus. Intramuscular administration results in a less abrupt onset and a more prolonged duration of curarization. With subcutaneous injection, absorption is irregular, unpredictable, but generally slower. No residual effects on the general body economy have been reported. However, an apparently cumulative or less transient effect on the myoneural apparatus is consistently observed. Since no adequate method of titration of blood levels is available, the basis of this clinical observation cannot be determined.

Ruskin and his associates²⁷ studied the electrocardiograms of curarized patients and found no change suggestive of a curare effect in therapeutic doses. Other reports in experimental animals and man corroborate this lack of a significant cardiovascular effect of pure tubocurarine. When curarization reaches levels beyond myoneural effects, there may be changes associated with involvement of the autonomic nervous system, or with the asphyxia of respiratory paralysis. Therapeutic applications require levels well below that required for the aforementioned effects.

IB. SHOCK THERAPY

In 1940, Bennett,²⁸ of Omaha, aware of the vast therapeutic opportunities inherent in the properties of curare, suggested its use in shock therapy and collected a series

of cases in which curare was used for the prevention of skeletal injury during shock therapy. His material was admirably presented and his technics are relatively unchanged to date. Curare unquestionably softens the convulsion incident to shock therapy,^{29,30} and thus aids the prevention of some of the common complications, such as crush fracture, etc.

Mode of Administration. An intravenous injection of an aqueous solution of curare is started two minutes before the shocking agent is applied. One mg. of curare seems to curarize effectively 2 pounds of body weight. The speed of injection influences the rate and degree of curarization.³¹

Although this form of therapy is widely used, it has not gained the universal acceptance given curare by the anesthesiologists. The explanation may well lie in the fact that the cases are very often handled under conditions far different from the operating theatre. Patients are treated most often in their own beds and given doses of curare that anesthetists might use with impunity. Premedication with atropine or scopolamine is rare and the period of observation frequently short. Indeed, one is struck by how few accidents have been reported in the literature.

Under the conditions outlined by the original workers,^{28,32} however, curare has been useful in the prevention of injury and in the protection of patients in whom shock therapy might otherwise be contraindicated.

Electroencephalograms obtained in patients before and during treatment have shown no variation which might be assigned to curarization,³³ except in the occasional dropping out of scalp muscle artefact. However, at certain levels during prolonged curarization a marked drop in brain wave potential has been observed. It is of interest that one observer has reported that, in spite of controlled respiration, there was consistent loss of consciousness in all patients

given critically large doses of intravenous curare preliminary to surgery.¹⁶

IC. TETANUS

Although tetanus in most western countries is a relatively minor problem, in the Middle East it is a formidable one. Extensive use of antitoxin alone does not prevent a high mortality. The period of abnormal motor activity or convulsion is poorly controlled by conventional medication and at great cost to body economy.

The use of curare in the amelioration of these convulsions requires great skill and constant observation. Prolonged curarization can result in a state similar to surgical shock.³⁴ Devoid of the pumping action of normally innervated muscles, the limbs act as reservoirs, with circulating blood reduced and shock eventually supervening. The prevention of this syndrome requires several prophylactic maneuvers. Before curare is administered, the patient must be carefully bandaged to prevent vascular pooling in the extremities. Likewise a snug scultetus binder should be applied to prevent splanchnic pooling incident to relaxation of the abdominal muscles. During treatment, blood volume must be followed closely and fluid intake and plasma volume controlled.

Curare therapy has proven of great value in tetanus. West,³⁵ Cullen,³⁶ among others, have contributed to the literature which contains many excellent studies.^{37,38,39,40,41,42,43,44} Others have documented the dangers inherent in the technic.³⁴ One line of approach takes advantage of the availability of aqueous (rapid-acting), and oil suspended (slow-acting) preparations.* The patient is curarized fairly rapidly with aqueous curare and the oil suspension added until an adequate base level is achieved. This level can then be supplemented by additional aqueous curare when necessary.

* *D*-tubocurarine chloride in oil and wax has been used, according to this technic, in five consecutive cases of severe tetanus with successful outcome.

The combination may be utilized in very much the same manner as are protamine zinc insulin and standard insulin.

II. USE OF CURARE TO OBTAIN A LISSIVE OR RELAXANT EFFECT WITHOUT LOSS OF VOLUNTARY STRENGTH

The experiments of Bremer and Titeca,⁴⁵ in 1927, and Hartridge and West,⁴⁶ in 1931, greatly extended our understanding of the nature of action and the clinical value of the drug. Bremer demonstrated that small, non-paralyzing concentrations had a specific effect on muscle "tonus." West, in 1931, described a lissive or relaxant action, accompanied by little or no loss of voluntary power. His clinical investigations included the use of curare in reducing spasticity and rigidity. This important work was badly hampered by the lack of a reliable preparation. He was fully aware of the variability of specimens and of the vast number of alkaloids of the same generic type but of differing effect. His investigations remain the groundwork of present day curare therapy of this type.

The availability of a preparation of standard properties in recent years has given great impetus to both physiological and clinical investigation. The aqueous solution has proven very efficient in the induction of neuromuscular block, as described previously. As a means of creating a transient partial block it has been much less satisfactory. Its usefulness has been sharply limited by its narrow therapeutic margin and evanescent effect, in spite of a sound physiological basis.

West,² Burman,⁴⁷ Bennett⁴⁸ and others have described the use of aqueous preparations in syndromes exhibiting spasticity, rigidity and involuntary movement. They noted demonstrable clinical reduction in abnormal activity. This effect, however, was usually exceedingly transient and therefore of questionable therapeutic value. In

cases of cerebral palsy, Denhoff and Bradley⁴⁹ found that the initial period of response to effective doses was characterized by masked facies, head drop and mental confusion. After these effects wore off, the useful clinical effect became evident.

These clinical investigations were carried out with aqueous solutions, administered intravenously or intramuscularly. Practically all observers have been unanimous in their dissatisfaction with the evanescent clinical response and the concomitant side reactions. Absorption is followed by high blood levels and rapid elimination. At those high levels, central and peripheral effects occur together. Along with relaxation, the classical signs of curarization supervene. These include dizziness, blurred vision, diplopia, head drop, asthenia and mental confusion. Prolongation of the desired effect at designated levels is difficult or impossible to achieve.

Long-Acting Preparations. In an attempt to prolong the desired action and avoid the unpleasant side-effects incident to uncontrolled concentrations, various measures have been tried. An oil and wax suspension, similar to that devised by Romansky⁵⁰ for penicillin, was prepared by Schlesinger⁵¹ in 1945 and first reported in a series of cases with spasticity following injury to the spinal cord. A series of 200 cases has since been reported by the same author.⁵²

This preparation consists of a suspension of 3 per cent *d*-tubocurarine chloride in 4.8 per cent white wax and peanut oil. It yields a slow-acting curare effect, lasting in some instances more than three days. With dosages which afford good clinical response in certain syndromes, no unpleasant curare side-effects are seen. Occasionally, during adjustment of dosage levels, blurring of vision, diplopia or dizziness has been noted.

In therapeutic dosage range, the drug has been singularly free of side-effects and

has shown no tendency to disturb normal body economy or cause habituation. Statistically, spasm, spasticity and rigidity are affected in order of decreasing efficiency. Dosage levels are complicated, and more strikingly related to the degree of motor acceleration than to body weight. Duration of clinical effect likewise seems inversely proportionate to the degree of motor abnormal activity.

Where partial block of neuromuscular conduction is desired, the usefulness of a long-acting preparation becomes apparent. In the syndromes to be described below, the availability of *d*-tubocurarine in oil and wax answers the previous objections to curare therapy. The patients in this series have largely been ambulatory and at their usual vocation.

IIA. MUSCLE SPASM

The term "muscle spasm" is widely and loosely used but very difficult to define. It may be considered as a state of transient contraction, not amenable to voluntary control, characterized by increased shortening reaction and usually associated with pain on attempted extension.

Clinically, the syndrome is well recognized. It may be a reaction to muscle irritation, inflammatory or traumatic. Frequently, it is reflex in origin and secondary to visceral disorders of like segmental nervous connections. Kellgren,⁵³ Wolff⁵⁴ and others have shown that reflex spasm may be perpetuated after cessation of the initiating stimuli. Such a picture is well represented by the vicious cycle of pain and spasm in low back injury. The initiating trauma is followed by muscle splinting, then pain, then further muscle splinting. Dramatic relief may be afforded by any agent which seems temporarily to break up the cycle. Heat, novocaine injections, etc., have at times served this purpose in individual cases.

Since curare is a physiological muscle relaxant, it is not surprising that muscle spasm responds so well. It has been consistently possible to break up true muscle spasm when the initiating condition is static or brought under control. Where the local pain and spasm are secondary to root compression, radicular pain persists after reduction of the reflex spasm. This response may be a useful clinical test.

IIB. SPASTICITY

Spasticity is characterized by increased excitability of the stretch reflex. Motion, passive or active, is accompanied by reactive muscle contraction which interferes with useful motor function. An attempt is made to saturate the patient with curare at blood levels which do not interfere with voluntary function but reduce stretch reflex sensitivity. This unmasking of voluntary power, if present, results in increased motor efficiency. Retraining is then imperative in order to rebuild muscle volume and useful habit patterns.

In *spastic paraplegia*, the use of curare in oil has proved a valuable adjunct to treatment. These cases have always been most difficult to handle, and no adequate measure has yet been described which will alleviate the distressing reflex manifestations of this condition with complete success.

In these cases it has been possible to: (1) reduce mass movements and thus aid healing of decubiti and prevent sudden expulsion of urine; (2) prevent contractures, and (3) permit active physiotherapy without acceleration of reflex spasm.

In *spastic paraparesis*, it is sometimes possible to relieve crippling spasticity without resort to surgery. Such surgical procedures take a toll in reduced motor power. Early rehabilitation of the patient is necessary to prevent deformity and atrophy. With good reduction in stretch excitability, the physio-

therapist can work to this end. Without such reduction, physiotherapy merely acts as a stimulant to reflex activity.

In spasticity, the duration of effect is of better than average duration and, in general, patients do not return to their original level of dysfunction if therapy is stopped.

Birth Injuries, Cerebral Diplegia or Spasticity with Dystonic Features. In his monograph on disorders of the central nervous system in children, Crothers⁵⁵ states: "... it is essential to develop every motor asset in sight. This conservation and development of assets is procured by two different but closely coordinated methods: First and always, by training, and second by procedures which avoid or correct contractures." Achievement of both these objectives is facilitated by the use of curare in oil. Training capacity is markedly enhanced by the reduction of abnormal activity, with a consequent increase in motor efficiency. The same reduction in spasticity or abnormal muscle tensions also allows a range of motion and activity which prevents further fixation deformity or contracture. Unlike surgical procedures designed to this end, it is unnecessary to destroy innervation or reduce the number of functioning motor elements contributing to the deformity. Effective diminution in abnormal motor activity can be obtained without perceptible loss of motor power.

One has only to watch these children at school to realize the titanic effort which goes into every attempt at motor performance. In light of this, the degree of their achievement under this form of therapy might seem slight to the casual observer. Nevertheless, by objective performance standards the improvement in motor performance is striking. The same tremendous drive which characterizes their usual effort now pushes their performance levels forward at rapid rates.

Improvement may be expected in the following sequence: (1) speech, (2) ability to sit quietly, (3) gait, (4) eating, writing, and performance of skilled motor activities. These patients have maintained their improvement on doses twice weekly.

IIC. RIGIDITY, AS IN PARALYSIS AGITANS

Evaluation of treatment in these cases is most difficult. It can be definitely stated that rigidity is an indication, tremor is not. Rigidity associated with extreme discomfort, immobility and beginning contracture can be partially alleviated. Sleep is usually improved. Pain associated with long standing muscle tension can be influenced to a gratifying degree. In rigidity there is, however, a wide disparity in response and in dosage tolerated.

It is not surprising that there should be such a wide variance between the effects in spasticity and in rigidity. Spasticity depends upon hyperexcitability of reflex mechanisms such as the stretch reflex, whereas rigidity is a function of simultaneous innervation of agonists and antagonists in addition to reflex mechanisms.

IID. DYSTONIA AND ATHETOSIS

It has been possible to: (1) reduce spontaneous movements so that patients can sit quietly for reasonable periods, (2) make active exercise and motor training possible, often for the first time, (3) improve sleep.

General Observations. Patients almost invariably note a pleasurable feeling of relaxation within two hours after injection. Under favorable conditions, in fact, most of them doze during this period. There is an associated fall in systolic pressure, averaging 20 mg. Hg, which is related to muscle relaxation and is not a specific vascular effect.

Recognizing the general sedative effect, a series of cases showing motor acceleration on a psychiatric basis has been treated. The early results are inconclusive at this time.

No toxic or side-effects of clinical significance have occurred in the therapeutic range. Once concentrations pass a critical level, however, central effects supervene, with mental confusion and a feeling of marked tenseness in addition to the classical toxic signs.

There have been no toxic effects on any organ system over long periods of time and no changes in body economy or general well being. No tendency to habituation has appeared in this series, although one patient has had more than seventy-five injections. Contraindications specifically are: (1) any myasthenic tendency and (2) kidney disease. Since curare is eliminated largely unchanged in the urine, poor renal function conceivably could elevate blood concentrations to a dangerous degree.

TUBOCURARINE IN OIL AND WAX

Method of Administration and Dosage Requirements. Crystalline *d*-tubocurarine chloride is suspended in peanut or sesame oil and white wax. The preparation in use today contains the equivalent of 175 units of standard curare per cc. The preparation is stable and can be sterilized repeatedly. The average dose is 1 cc. \pm 0.25.

Intramuscular injection in the gluteus is most frequently used, although when a patient is well saturated, the subcutaneous route may be used for its slower absorption curve. Dosage is determined by clinical observation, the most efficient below loss of voluntary motor power being chosen. Duration of effect is likewise gauged clinically, the greater number of patients requiring injections every seventy-two hours.

Where possible, electromyography is utilized to check the change in stretch reflex as an objective index of effectiveness of dosage levels.

Technical precautions are: (1) prevention of dilution by fluid in syringe or needle, (2) choice of site of injection away from

vascular channels, (3) vigorous shaking to prevent dropping out of suspension, and (4) avoidance of massage of area of injection.

HF. USE OF CURARE IN STATES RESEMBLING SPASM AND SPASTICITY AS IN POLIOMYELITIS

The treatment of acute and subacute anterior poliomyelitis consists largely in the alleviation of symptoms and the prevention of deformity and loss of motor function. The fact that there is no specific therapy perhaps throws undue emphasis on forms of symptomatic relief.

During the early phases of the disease or acute febrile illness, meningeal inflammatory reaction occurs, accompanied by root irritation. This is followed by what appears to be muscle spasm. Certainly root irritation is capable of initiating hyperesthesia and reflex muscle spasm. In addition, there may be actual inflammatory reaction in the muscles per se characterized by muscle shortening, resistance to stretch, pain and tenderness. A similar picture is seen in acute rheumatoid arthritis. Spasticity also can be elicited at times and seems to be present when the muscles are studied electromyographically. The exact definition and mechanism of these states resembling spasm and spasticity is not completely clear. Bodian recently has demonstrated spasticity in the experimental animal following intracerebral inoculation of virus. Such studies may afford a much needed clarification of the underlying pathological processes.

The similarity of the clinical picture to true muscle spasm and spasticity makes a trial of curare a rational procedure. Ransohoff,⁵⁶ and subsequently Fox⁵⁷ have reported a series of such trials. The former reports marked reduction in pain, relief of muscle spasm, and earlier capacity for exercise following the use of curare in aqueous solution. Dosage requirements are obviously complicated by variations in the

clinical picture but the basic schedule used is 0.9 unit per kilo of body weight. Fox finds curare a dangerous tool and one difficult to evaluate. Obviously further investigation is required. The usefulness of slower-acting, and probably more easily controlled, oily suspensions of the drug is undergoing detailed study.

Ransohoff adds to the description of the use of curare a therapeutic code of his own, namely, active motion in spite of severe pain. One must be careful to judge this refinement of therapy on its own merit rather than to consider it an integral part of curare therapy in poliomyelitis.

PROSTIGMIN AS A DEPRESSANT OF NEUROMUSCULAR CONDUCTION

The fact that prostigmin and curare are, at least in part, pharmacological antagonists makes the recent literature on prostigmin of special interest. Since 1940^{58,59,60} there have been successive reports on the use of prostigmin, or physostigmine and atropine in a variety of conditions including muscle spasm, spasticity, contracture, muscular pain, weakness, incoordination and fatigue in chronic rheumatoid arthritis, following fractures and other injuries, hemiplegia, spastic cerebral palsy, subacromial bursitis, facial paralysis, stiff neck and low back pain.

The description of a beneficial effect of prostigmin as a depressant of neuromuscular activity at first appears paradoxical to one familiar with the conventional pharmacological concepts of prostigmin effects. Kabat, and his associates, however, have prefaced their clinical presentations with an interesting hypothesis as to its mode of action. The experiments of Schweitzer and Wright^{61,62} in 1937 form the basis of the theory. These investigators found that the usual effects of prostigmin did not occur under certain laboratory conditions. If, in an experimental animal, (*the blood supply to*

the limbs was completely cut off) and then prostigmin was given intravenously, there was a depression of the patellar jerk. However, with an intact general circulation no such phenomenon occurred. Schweitzer and Wright postulated a depressant action of the drug on the isolated spinal cord to account for their findings. They were careful to point out that a similar amount of prostigmin injected subcutaneously or intramuscularly had no such depressant effect on the reflexes. In a later study (1937) they found that when injected intravenously into un-atropinized animals in doses of 0.5 mg., prostigmin slightly "depresses the knee jerk, and may completely abolish it for many minutes in doses of 1 mg." With the circulation to the limbs cut off they found that 1.5 to 3 mg. of prostigmin injected into the jugular vein produced a diminution or abolition of the knee jerk. They conclude that, "As the peripheral action of prostigmin on muscle is excitant there can be no doubt from the above results that prostigmin exerts a direct inhibitory influence on the central nervous system."

Several points are at once obvious. With intravenous doses of 0.5 to 3 mg. in animals as a basis, a comparable amount in the human would be well above that generally used, and actually in the range of toxic peripheral depressant effects. In the paper by Kabat the maximal dose mentioned is 3 cc. (1.5 mg.) given *intramuscularly*, or 45 mg. by mouth three times a day. Absorption and utilization of prostigmin given orally is notoriously inefficient. Even by mouth, sensitivity occurs very frequently below the maximum level mentioned above. Neither intramuscular nor mouth administration meets the criteria of Schweitzer and Wright's experiments.

For these and other reasons, the experiment is not a critical one necessarily applicable to human physiology. It may be concluded that these interesting studies are

insufficient to explain the reported effects of prostigmin on neuromuscular conduction in the various syndromes mentioned above. Nevertheless, reports of the excellent results achieved with this form of therapy make further study imperative. Unfortunately, there has been opportunity for group study in only certain of the types of pathological conditions represented in the original reports.^{63,64}

At the American Rheumatism Association Meeting in May, 1946, Balboni⁶⁵ and his associates presented their results in a large series of carefully observed patients with rheumatoid arthritis in various stages. They reported no useful therapeutic effect with long trials of prostigmin. Discussion on the floor unanimously supported their findings. The clinical data presented by a large group of investigators were overwhelmingly against any therapeutic value of the drug in the treatment of rheumatoid arthritis. Cohen and Trommer,⁶⁶ and also Kabat,⁶⁰ believe that chronic arthritic changes respond more favorably than acute. This is surprising since one ought logically to expect acute muscle spasm and early deformity to be easier to influence than long term contracture associated with fibrosis.

Increased utilization of prostigmin in the various syndromes described by Kabat and his group will ultimately define its clinical usefulness. Further laboratory investigation of its mode of action is likewise desirable.

ANTIDOTAL NATURE OF ANTICHOLINESTERASES

It has been repeatedly demonstrated that the anticholinesterases, such as physostigmine and prostigmin, are in certain concentrations, physiological antagonists of curare.^{67,68} When applied to the curarized or partially curarized striated muscle preparation, they will evoke a return of electrical and mechanical response. However, when curarization has progressed to intense cen-

tral effects, the anticholinesterases do not seem to act in this way, and may, indeed, increase the severity of the poisoning. Koppanyi and Vivino⁶⁹ have reported experiments delineating the limits of the antidotal action of these drugs and show that increasing their doses does not increase antidotal action beyond a certain point. The addition of ephedrine or tyamine specifically increases the neutralization effect in their experiments.

Pick and Unna⁷⁰ found that with levels of tubocurarine which abolished cortical electrical potentials in the frog, prostigmin restored motor activity but did not influence the cortical depression.

Prostigmin itself caused a similar drop in cortical potentials. They concluded that curare and prostigmin were antagonists in myoneural junction action but that their central effects were similar. On this basis, prostigmin would be contraindicated as an antidote in severe curare intoxication.

CONCLUSION

The availability of a pure curare alkaloid, tubocurarine, has accelerated experimental and clinical exploitation of its unusual properties. Unquestionably, a great deal remains to be learned. The most pressing problem is clarification of its mode of action at the myoneural junction. A method of assaying blood levels is badly needed, as is further elucidation of its central versus peripheral effects, and its true relationship to the anticholinesterases.

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Seminar on Antibiotics

Chemotherapy and Antibiotics in the Treatment of Meningitis

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IN the history of medical therapeutics there have been few more dramatic events than the influence of chemotherapy and antibiotics on purulent meningitis. A decade ago cerebrospinal fever, in spite of specific serum therapy, was still a grave disease with a high case-fatality rate. Meningitis due to *H. influenzae* was almost invariably lethal, and recovery from pneumococcal or streptococcal meningitis unknown. Now, as a result of new agents in treatment, cerebrospinal fever is a brief disease, usually without sequellae, and carrying an almost negligibly small case-fatality rate; moreover, recovery from the other varieties of purulent meningitis can occur in the majority of cases. These results, of course, have been achieved by sulfonamides, penicillin and streptomycin, but they cannot be approximated without a considerable knowledge of the diseases in question, together with technical skill in management. It is the purpose of this review to discuss the technics of these new treatments.

CEREBROSPINAL FEVER (MENINGOCOCCAL MENINGITIS)

Cerebrospinal fever is the commonest of the so-called primary meningitides. In this instance the use of the term "primary" is a poor one, for the meningitis is often preceded by a well defined catarrhal, and

septicemic state. One speaks of it as primary merely to differentiate it from a condition like pneumococcic meningitis, which is ordinarily secondary to lesions such as skull fracture, mastoiditis, etc.

The causative agent of cerebrospinal fever, *N. meningitidis*, is an organism which has a peculiar predilection for the coverings of the brain and spinal cord. It is not particularly pathogenic for the upper respiratory tract. It can be recovered on culture from the nasopharynx of healthy carriers who have never had the disease, and under normal conditions, when the disease is not epidemic, such healthy carriers may be as high as 5 per cent of urban populations. Presumably the appearance of sporadic cases is due to this fact; either the healthy carrier himself contracts the disease, or else he passes on the organism by expelled droplets to another individual whose resistance is sufficiently low so that invasion occurs. In either case, implantation in the meninges takes place by way of the blood stream, and this may or may not take the form of a clearly defined septicemia with fever, purpuric rash and a positive blood culture. Sporadic cases are seen in all large cities during the winter months, and the case history will yield no clue as to the source of the infection. In contrast to this, the disease may also take on epidemic proportions, particularly under circumstances

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when large groups of susceptibles are herded together. As susceptibility decreases with age, it follows that localized outbreaks are most often seen in institutions for the young, Army camps, and the like. At such times, bacteriological surveys have shown that the carrier-rate becomes very high. The clinical severity of the disease varies in different years and different epidemics, and it was observed in the days of serum treatment that the case fatality rate varied rather widely even when potent anti-serum was employed.

These epidemiological findings have been briefly sketched in to emphasize the fact that cerebrospinal fever may occur anywhere and at any time. Unless every physician bears this constantly in mind, patients will continue to die needlessly of meningitis, for the key to success in this disease is *early diagnosis together with prompt and vigorous treatment*. And the only means of early diagnosis is to suspect meningitis in every patient who is taken acutely ill. This may sound like a rather extravagant statement, but it is the author's conviction that priceless time is continually being lost, not because physicians are ignorant of the florid picture of the disease, but because the more subtle, early danger signals escape notice simply owing to the doctors' failure to think of meningitis. This is not the place for a systematic consideration of the signs and symptoms of the disease, but a few points in regard to early diagnosis are worthy of mention. First, it must be borne in mind that meningococcic infections almost invariably provoke a leucocytosis. Now, apart from lobar pneumonia and streptococcal throat infections (the nature of which should be fairly obvious) the vast majority of ordinary acute febrile diseases are *not* accompanied by a leucocytosis. Thus, a young individual who has a chill followed by fever, a macular rash tending to become purpuric, and a high white blood count, is

almost certainly in the septicemic stage of cerebrospinal fever. It is *not* measles. If treatment is delayed until frank meningeal signs appear, very valuable time will be lost. Even in the absence of the characteristic exanthem of cerebrospinal fever, the disease must always be considered a possibility in acutely ill young people showing a leucocytosis. Now it is obviously impractical to do a blood count on all cases of common respiratory infections during the winter months. But if certain warning signals are kept in mind, blood counts will be done where needed. These are as follows: repeated vomiting, very severe headache, mental dullness and confusion should put the doctor on the alert. These symptoms are *not* characteristic of common upper respiratory infection, and they are indications for a leucocyte count. They are also indications for a very careful search for meningeal signs and a lumbar puncture, if any grounds for suspicion exist.

The meningococcus is exceedingly sensitive both to sulfonamides and penicillin, but in deciding how these agents are to be used, singly or in combination, certain elementary facts must be remembered. Sulfonamides (of which sulfadiazine is probably the drug of choice) are easy to administer, and they penetrate into the cerebrospinal fluid in high concentration. They may, however, produce dangerous side effects. Moreover, there is a time lag of a few hours before they begin to exert their influence. Penicillin, on the other hand, probably begins its action more promptly and it is almost wholly non-toxic. But unless given in enormous doses parenterally, comparatively little makes its way into the subarachnoid space. It is generally agreed, therefore, that in meningitis it must be given intrathecally, and this naturally implies repeated lumbar taps. With this background, let us consider the ideal treatment of the disease.

This writer believes that sulfadiazine, because of its great efficacy (as shown in many thousands of patients treated in the Army with this drug alone), its ease of administration, and high penetration into the cerebrospinal fluid, still remains the most valuable single agent in cerebrospinal fever. That penicillin also has a place of great importance is equally true, and this point will be made clear in the ensuing consideration of several clinical categories of disease.

Mild to Moderate Cases Treated Early. A very wide experience indicates that sulfadiazine alone is wholly adequate in the treatment of this variety of case. An outline of treatment is as follows: Lumbar puncture for diagnosis; fluid to be sent for cell count, smear, culture, sugar; blood culture. Immediately after these are completed, give 5 Gm. of sodium sulfadiazine dissolved in a liter of normal saline by fairly rapid intravenous infusion. As the patient is often somewhat dehydrated, this may well be immediately followed by more intravenous fluid at a slower rate. If sodium lactate is available, 500 to 1000 cc. of a 1/6 molar solution may be administered in the second infusion in order to achieve a rapid alkalinization of the urine; for it must be remembered that where sulfonamides are employed in large dosage, the danger of precipitation in the urinary passages is not inconsiderable. It also goes without saying that the usual alertness to the possibility of toxic side effects must be maintained with repeated observations of the blood count and urine.

The object of treatment with sulfadiazine is the rapid establishment and maintenance of a satisfactory blood concentration of the drug, preferably in the range of 12 to 15 mg. per cent. The only way this can be determined is by having the blood level estimated, a procedure which, in a serious infection like meningitis, is well worth carrying out. By our initial infusion we

have probably achieved this level. Let us estimate it, say, at six or eight hours after the beginning of treatment, and guide our future dosages accordingly. If at this time the patient can take medication by mouth, it can be continued in the form of 1.0 to 1.5 Gm. (or even higher if necessary) every four hours. The customary forcing of fluids should be employed, and 2.0 Gm. of soda bicarbonate may be given with each dose of sulfadiazine to maintain urinary alkalinity. The drug, of course, can be continued by the intravenous route, but in the majority of mild cases the single initial infusion will suffice.

The expected result with this treatment is a noticeable improvement in clinical symptoms usually perceptible six to twelve hours after therapy is instituted. In twenty-four hours there is usually marked improvement and the fever has diminished. Stiff neck will ordinarily persist for two to three days, but at the end of forty-eight hours the patient should be otherwise asymptomatic. Failure to obtain this result usually means that dosage has been inadequate, although the possibility of an accelerated sulfonamide reaction in a sensitive individual must be kept in mind.

Treatment with sulfadiazine alone then, in the mild to moderate case, is simplicity itself. A satisfactory drug level is established and maintained, together with the usual sulfonamide precautions. One or two other points deserve comment, however. The first is the duration of treatment. While it is probable that cure of the disease takes place very rapidly, it is best to maintain treatment longer than may be strictly speaking necessary. A week is, in my opinion, the minimum. The second point relates to lumbar punctures. It is my belief that after the first diagnostic tap, lumbar puncture need be performed for only two reasons, the relief of symptoms (persistent headache, vomiting, nuchal rigidity, respiratory difficulty),

or to appraise the meningeal situation in a case in which the expected good result apparently has not been achieved. In other words, the majority of patients can be handled quite satisfactorily with but the single initial diagnostic tap.

This is a brief outline of treatment of the ordinary case of cerebrospinal fever with sulfadiazine alone. The majority of patients can be treated in this way. Before going on to discuss the more severe types, it is worth mentioning that in an occasional mild case of cerebrospinal fever sulfadiazine may be contraindicated. The aged sometimes tolerate the drug rather poorly; in the presence of renal insufficiency, extra caution must be employed with sulfadiazine; these are indications of the type of case in which a physician may prefer to use penicillin alone, as he most certainly would if dealing with a patient known to be sensitive to sulfadiazine.

Severe Cases, or Cases in Which Treatment Has Been Delayed. By these terms are meant either a patient with an unusually violent onset, early delirium, stupor, etc., or one who has evidently been in the meningitic stage for some considerable period of hours before treatment can be started. It may be remarked that before the advent of penicillin, large numbers of patients in these categories were cured by sulfadiazine alone. With the antibiotic at hand, however, there are theoretical as well as practical indications for its use. An intrathecal injection of penicillin should be made through the lumbar puncture needle immediately after withdrawal of the fluid for diagnostic study. It is probably wise not to exceed 25,000 or 30,000 units; this may be dissolved in 4 or 5 cc. of saline and injected slowly and gently, with intermittent withdrawal of spinal fluid into the syringe so that further dilution is effected. At the same time, if there are marked evidences of septicemia, a large dose, say 200,000 units, may be given

intramuscularly. Meanwhile, sulfadiazine treatment is instituted and maintained as in mild or moderate cases. If it is deemed necessary to repeat the lumbar tap later for symptomatic relief, a second intrathecal injection of penicillin may be made. It might be wise also to repeat the intramuscular injection after three hours. Thenceforward the patient may be carried on sulfadiazine alone. By these means, the full immediate effect of penicillin is obtained both locally and systemically during the latent period before the sulfonamide begins exerting its effect.

Maximally Severe Cases (Waterhouse-Friderichsen Syndrome). The so-called Waterhouse-Friderichsen syndrome consists of a state of shock accompanying profound sepsis. It is most often seen in overwhelming meningococcic infection. Clinically, it is characterized by the sudden appearance of a profuse purpura together with very low blood pressure, at shock level, tachycardia, anuria, etc. In addition, infection of the central nervous system has ordinarily taken place, and one usually sees delirium or coma with some meningitic signs. Here is a medical emergency in which time is of the essence, and there is no doubt that an occasional case conforming to this pattern will be lost in spite of the best possible care. On the other hand, there are now abundant examples of the so-called Waterhouse-Friderichsen syndrome, hitherto regarded as a condition utterly without hope, in which recovery has taken place with modern treatment.

One may repeat, time is of the essence. A large intramuscular dose of penicillin should be given as the patient is being prepared for lumbar puncture. The treatment of the infection proceeds along the lines suggested for severe cases, except that intramuscular penicillin in large doses should be continued at three-hour intervals for two or three days, and that higher blood levels

of sulfadiazine, i.e., around 20 mg. per cent, should be aimed at. It is also probably wise to repeat lumbar punctures with intrathecal antibiotic twice daily for a couple of days. But there is an additional indication for treatment here of the utmost importance, i.e., the treatment of shock. For this purpose it will probably be necessary to employ transfusions of blood or plasma, and if the blood pressure is not materially restored by the initial intravenous infusion of sulfadiazine in saline, either whole blood or plasma should be given immediately. These measures should be repeated later if necessary.

In cases of this sort the question usually arises, should adrenal cortical hormone be given? This is based on the frequent association noted at the postmortem examination of massive adrenal infarction with the Waterhouse-Friderichsen syndrome. It seems to me, however, that one does not need to explain the shock on the basis of adrenal insufficiency. For one thing, it comes on too fast. For another, many cases have been described in which profound shock occurred in the presence of a comfortable supply of anatomically normal adrenal tissue. My own belief is that this debate is an academic one. Most certainly, patients with the Waterhouse-Friderichsen syndrome have survived when the shock was treated by simple methods. Equally certain is it that the patient will ultimately die if all his adrenal tissue has been destroyed. However, adrenal cortical hormone will probably do no harm and may be used.

The foregoing paragraphs are intended to outline a more or less ideal scheme of treatment of various categories of cerebrospinal fever. By the use of such methods, in circumstances in which early diagnosis is feasible, the case fatality rate can probably be reduced to less than 2 per cent. It was about 2 per cent for the year 1944 in the United Kingdom Base among American

soldiers, and no doubt this figure can be somewhat improved. One additional point is of sufficient interest to warrant mention. So great is the sensitivity of the meningococcus to sulfadiazine that one or two small doses are sufficient to eliminate the carrier state. Thus, when cerebrospinal fever breaks out in a dense population, such as an Army camp, a few small prophylactic doses administered to the whole command will arrest the epidemic at once.

PNEUMOCOCCUS AND HEMOLYTIC STREPTOCOCCUS MENINGITIS

These conditions will be considered next because their treatment is so similar to that of cerebrospinal fever. It is essential first, however, to speak of an important difference in pathogenesis. As has been indicated above, cerebrospinal fever is a "primary" type of meningitis, i.e., it is not secondary to an adjacent or remote suppurative process, although it is preceded, presumably in all cases, by blood involvement, even if this be not apparent. On the contrary, in pneumococcal and streptococcal meningitis, the physician must be constantly on the look-out for a focus which may need surgical therapy. Both diseases may arise secondarily to a simple septicemia, but they are more likely to occur as a result of a contiguous lesion. Fractures through the base of the skull entering a contaminated sinus are examples of this. Otitic infection, usually with mastoiditis, is another. Occasionally, they arise following suppurative sinus disease. There is always the possibility of an associated suppurative lateral or cavernous sinus thrombosis. Brain abscess may coexist. Now local areas of suppuration such as these are not very favorably affected by parenteral sulfonamide or antibiotic treatment; and, if they continue to feed organisms into the meninges, treatment will not avail. They must be searched for, located and drained. It follows, therefore, that an

internist who is treating meningitis due to either pneumococcus or streptococcus will almost always need the collaboration of an otologist and occasionally of a neurosurgeon.

There is another point of difference which bears on the treatment. Both of these organisms produce a much more severe meningitis, apart from the associated lesions, than does the meningococcus. Even before any specific therapy there were some recoveries from cerebrospinal fever; perhaps 20 per cent survived the disease though often with permanent sequellae. This did not occur with pneumococcus or streptococcus. Pathologically, they produce a more severe lesion. The exudate is more abundant, more plastic. Fibrin formation is marked, with a great tendency to blocking of aqueducts and foramina. There is also a rather marked tendency to perivascular inflammation, extending down into the brain substance, with vascular thrombosis, which does not usually occur in cerebrospinal fever. These facts have an important bearing on our thinking in regard to the intensity and duration of treatment.

Pneumococcic Meningitis. The technics of sulfadiazine and penicillin therapy are the same as in severe cerebrospinal fever except that they are employed more intensively and for a longer period. Thus lumbar punctures with local injection of penicillin should be done twice daily for a week, and once daily for the next week. Penicillin in 200,000 unit doses intramuscularly every three hours should be continued for two weeks, although the dose may be cut in half at the end of the first week if the patient is doing well. Sulfadiazine levels of 15 mg. per cent are maintained. As to duration of treatment, there can be, of course, no set rule. But it seems a wise general principle to maintain it much longer than seems necessary. My inclination is to keep up local and parenteral penicillin for two weeks, and sulfadiazine for an additional week, if

tolerated. (If not, intramuscular penicillin should be kept up for that period.) After all, we are dealing here with a very grave and treacherous disease, and one in which relapses have been observed when treatment has been discontinued too soon.

Another question which is sure to arise is whether to give of type-specific anti-pneumococcus serum. My own feelings on this point might be indicated as follows: If an immediate typing has been made from the spinal fluid so that one knows the type at the very outset, if a supply of highly purified rabbit serum of the appropriate type is at hand, if the clinical picture is extremely grave, I am inclined to give a single intravenous dose. Usually these requirements are not met, however. There is apt to be a considerable lapse of time before one can give this treatment. Then, if the patient appears to be doing well, I am disinclined to risk an immediate serum reaction or serum disease later to complicate the picture during convalescence.

It has been suggested that the use of an anticoagulant, such as heparin, might be indicated with a view to lessening fibrin formation on the coverings of the brain. From a theoretical point of view this notion has much in its favor. But it must be remembered that heparinization will greatly complicate an already complicated problem in therapeutics, and that it must be interrupted if any surgery is undertaken, which is apt to be the case. I have seen one or two patients so treated with success, but there are a great number of equally successful cases in which no anticoagulant has been used.

One object of the anticoagulant, obviously, is to prevent block in the circulation of the cerebrospinal fluid. Should this complication develop in any type of meningitis, it is probably too late for heparin to be effective. Under these circumstances the condition should be promptly recognized

and an endeavor made to treat the internal hydrocephalus by cistern and ventricular punctures, as indicated, and the instillation of antibiotic by these routes.

With the introduction of the first sulfonamide effective against the pneumococcus (sulfapyridine) the first reports of cure of pneumococcic meningitis began appearing in the literature. With the use of this agent alone, perhaps 20 per cent of patients might be expected to survive. By means of the combined penicillin-sulfadiazine regimen of the type outlined above, the percentage has materially risen. It may now be in the neighborhood of 75 per cent.

Hemolytic Streptococcic Meningitis. The same principles apply here as in pneumococcic meningitis. Streptococcic meningitis is, however, a somewhat milder disease, and the intensity of the treatment may be lessened without danger. With sulfonamide alone the recovery rate was about three times as high as in pneumococcic meningitis. It would seem justified, therefore, to advise a slightly less vigorous regimen. Lumbar punctures may be done daily for a week with injection of penicillin, and then omitted if the clinical course warrants. Penicillin might be given in 100,000 unit doses every three hours after the first day. But I should be inclined to keep it up for a fortnight and the sulfadiazine for three weeks, as in the case of the pneumococcic infection.

H. INFLUENZAE MENINGITIS

Unlike the two varieties just discussed, *H. influenzae* meningitis is not usually associated with trauma or a nearby suppurative focus. It, therefore, may be described as "primary," although some degree of pharyngitis probably precedes infection of the meninges. Thus it resembles cerebrospinal fever clinically except that the rash, frequently seen in the latter condition, does not occur, and careful bacteriological examina-

tion of the fluid is necessary to differentiate the two. *H. influenzae* meningitis is almost wholly limited to infants and young children and is by no means uncommon. In fact, it has been stated to account for nearly a quarter of all the purulent meningitis in this age group. It was early recognized that the *influenzae* bacilli causing meningitis showed more serological specificity than the common respiratory strains, but it remained for Pittman¹ to demonstrate that meningeal organisms were encapsulated, and fell into well defined type-specific groups. It is now known that nearly all *H. influenzae* meningitis is caused by a type designated by Pittman as "b." These discoveries led to the therapeutic trial of specific antiserum. Early endeavors in this direction with horse serum were not very successful. The great advance in serum therapy was made by Alexander when he introduced highly concentrated type-specific rabbit antibody solution. At about the same time it was noted that sulfonamides had an action against *H. influenzae*. Of the sulfonamides, by far the best is sulfadiazine. The ideal treatment, as worked out by Alexander, consisted in a combination of the two agents.

H. influenzae meningitis is almost exclusively a problem in pediatrics, and for the complete description of Alexander's combined serum-sulfadiazine treatment the reader is referred to her most recent paper.² Essentially, it consists in the parenteral administration of 0.1 Gm. of sulfadiazine per kg. of body weight, accompanied by the intravenous administration of a single dose of antibody solution. The dosage of this is regulated by the severity of the infection (as judged by spinal fluid sugar levels), and ranges from 25 to 100 mg. of antibody nitrogen. The sulfadiazine is repeated at twelve-hour intervals until the patient can take the drug by mouth. By this method the case fatality rate was reduced to about 25 per cent in quite a large series of cases.

Since these advances were made a new antibiotic, streptomycin, has been introduced, which is effective against many gram-negative organisms insensitive to penicillin. Among these is *H. influenzae*. Streptomycin has, therefore, been tried in the treatment of influenza bacillus meningitis with very encouraging early results. Final appraisal of the drug is yet to be made, but Alexander's present scheme of therapy is as follows:³

As soon as the diagnosis is made—and here again one must repeat that accurate bacteriological study of the spinal fluid is *essential*—the child is started on streptomycin. In mild to moderately severe cases, this is the only form of treatment used (by mild to moderately severe is meant those patients with spinal fluid sugar over 15 mg. per cent). The drug is administered both intramuscularly and intrathecally, the twenty-four-hour dosage in the former category being 20,000 units per pound of body weight; this is divided into eight doses injected at three-hour intervals. By the intrathecal route 25 to 50 thousand units in a volume of about 5 cc. are given daily.

If the case is clinically very severe, or if the spinal fluid sugar is below 15 mg. per cent, combined serum-sulfadiazine treatment is given in addition to the above. So also are all three agents to be used if a good result is not obtained by streptomycin alone, or if the organism should develop strepto-

mycin resistance. From early observations on this method of treatment it seems likely that the case fatality rate in *H. influenzae* meningitis will be still further materially reduced.

OTHER VARIETIES OF PURULENT MENINGITIS

The four micro-organisms discussed above cause in the aggregate the great majority of cases of purulent meningitis. It is quite rare for infection of the meninges to be due to other bacteria. And yet virtually every pathogenic organism has at one time or another been described as causing meningitis. It is, let me repeat, for this reason that careful bacteriological study of the spinal fluid is so essential. The treatment of other types of purulent meningitis is dependent on a knowledge of the organism in question and follows the lines already described; that is to say, large doses of parenteral sulfadiazine are given—assuming the organism has any sensitivity to it—and the appropriate antibiotic is administered by the intrathecal and intramuscular route. As in the case of pneumococcus meningitis, it is probably wise to maintain treatment for a long period of time.

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Conference on Therapy

Treatment of Coronary Artery Disease

(Concluded)*

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy* by The Macmillan Company. The next report will appear in the January, 1947 issue and will concern Treatment of Rheumatic Fever.

DR. HARRY GOLD: We had a session on the treatment of coronary artery disease last week. There was not time enough to consider as many of the questions in need of an airing as we had hoped. It is for this reason that we are now holding the second conference on the same subject.

We had been having all the discussion from the front rows. How about the back rows today?

INTERNE: What is your opinion about the length of time one should keep patients with coronary thrombosis in bed?

DR. GOLD: Dr. Pardee, how long should patients with coronary thrombosis remain in bed?

DR. HAROLD E. B. PARDEE: It depends on the individual patient. It is about six weeks for most of them. There are some, however, who are so seriously ill that complete rest for a longer time is necessary. There are still others whose attack is obviously so mild that they may be allowed out after four weeks.

DR. GOLD: You do not sit them up in a chair in two weeks?

DR. PARDEE: I do not. I would not consent to the patient getting out of bed. I have occasionally allowed patients to get out of bed so early against my better judgment, because there seemed to be nothing else to

do and there was no harm from it. That is, of course, in cases of a minor attack.

DR. GOLD: Do you not think that the patient sometimes has a pretty hard time of it on a bed pan and struggles more there than on a commode?

DR. PARDEE: Yes, I do let him use the commode under those circumstances.

DR. GOLD: It is a fact then, that you do sometimes get them up out of bed at the end of five or six days, is it not?

DR. PARDEE: Yes, but that is not the same as having the patient out of bed all the time.

DR. CARY EGGLESTON: I think it is a very important point that Dr. Gold makes about the strain of using a bed pan. That differs with different individuals. But, there are many to whom, in my opinion, the strain of using the bed pan is immeasurably greater and more trying than the commode at the side of the bed. Under such circumstances, I surrender to the commode promptly.

DR. HAROLD J. STEWART: You would feel much worse if a patient died on a commode than if he died on the bed pan because he was out of bed.

DR. GOLD: There is indeed the problem implied in Dr. Stewart's remark. However, the fact remains, as pointed out in one of

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the previous conferences, that sitting in a chair involves no more burden on the heart than lying in bed, and it offers many advantages. The prejudice in favor of the bed has the support of long tradition and is difficult to overcome, but I firmly believe that the chair deserves a more prominent place in the management of the problems of acute coronary thrombosis.

DR. GOLD: Dr. Eggleston, what proportion of the patients with coronary thrombosis that you see, do you treat from beginning to end without a single drug, morphine or anything else?

DR. EGGLESTON: Virtually none.

DR. GOLD: You give them all morphine?

DR. EGGLESTON: No, but the vast majority of them get morphine.

DR. GOLD: Even if they do not have pain?

DR. EGGLESTON: In the acute stage, I think that the majority of patients require an opiate. In the first place, they are scared even if they have no very severe pain, and the calming influence of an opiate seems to me unequalled by any of our other sedatives. Therefore, I usually give them one or two doses of an opiate, and I prefer morphine or one of the other purified alkaloids.

DR. GOLD: It is my impression that in patients with coronary thrombosis doctors have gone to an extreme in the use of morphine. They often give it as a routine even when the patient is symptom-free. The doses are often too large. The intervals between doses are too short. The length of time doses are continued is too long. The result is an unjustifiable amount of morphine poisoning and dependence, vomiting, distention, urinary retention, respiratory depression, confusional states and the various other disturbances associated with this group of drugs. One should not give more than 15 mg. ($\frac{1}{4}$ gr.) intramuscularly as the first dose and at least one-half hour should elapse between doses. The larger the dose the more likely it is to cause vomiting and this in-

volves the very type of violent muscular activity we go to so much trouble to avoid in the acute phase. More than a total of 60 mg. (1 gr.) is rarely, if ever, justified on the first day. If that fails to abolish the pain, larger doses will also fail to do so, but will tend to induce a state of coma with dangerous respiratory depression. It is disconcerting to begin treating a patient for coronary thrombosis and to end by treating him for morphine poisoning. I think that situation is not rare. I have also seen some ambulant patients after an acute coronary episode going along with one or more daily doses of pantopon, dilaudid or spasmalgin. The difference in name seemed to have lulled the physicians into a false sense of security, or perhaps they were not aware of the fact that these represent morphine or its equivalents. Those that I saw were all addicted.

DR. EGGLESTON: I agree fully. I stop the morphine just as soon as pain and great anxiety disappear, and I substitute for the morphine one of the non-opiate hypnotics if they cannot sleep or if they are restless.

DR. GOLD: I believe that in general, not only morphine but other sedatives are used too freely in patients with coronary thrombosis. To keep them in a state of prostration, stupor or confusion by these agents seems to me a source of harm rather than good. Let them be without drugs if they are substantially free of symptoms.

INTERNE: Has demerol a place in the treatment?

DR. PARDEE: I have not as much faith in demerol as I have in morphine. Therefore, I have not used it in these cases. I have used demerol in other types of cases, and there I formed an opinion that it is less effective than morphine.

DR. GOLD: There is no doubt that demerol relieves pain and does so well in many cases of coronary thrombosis in doses about 7 to 10 times that of morphine, about 100 to 150 mg. of demerol in the place of

15 mg. of morphine. The two drugs, however, are not fully interchangeable. I know of one situation in which the patient, subject to severe and frequently recurrent attacks of cardiac pain, which were not relieved by nitroglycerin, secured prompt relief for a few hours from 100 mg. of demerol subcutaneously. He continued to use it quite frequently during a period of about two years and acquired both a tolerance and dependence. In one attack he took 100 mg. every hour for 5 doses which brought no relief but caused marked unrest. A dose of 15 mg. of morphine subcutaneously provided prompt relief in this situation. He had always avoided morphine because it invariably produced urinary retention requiring catheterization. Remember, demerol has a potentiality for addiction.

DR. McKEEN CATTELL: I would like to ask whether anyone here uses drugs to prevent premature beats or ventricular fibrillation, since that is apparently a serious aspect of coronary occlusion. Do you ever use aminobenzoic acid or some of its esters, which have been shown to decrease the liability to ectopic rhythm in the case of various drugs, such as epinephrine, ether, chloroform?

DR. GOLD: Dr. Stewart, have you any opinion about that?

DR. STEWART: No.

DR. GOLD: Dr. Pardee, do you do anything to prevent ectopic rhythms in a patient with coronary thrombosis?

DR. PARDEE: I usually give a fair amount of atropine sulfate with the initial morphine, that is, 0.8 mg. ($\frac{1}{75}$ gr.). I do not repeat that unless an arrhythmia appears. In such patients, I continue the atropine 0.6 mg., at about four-hour intervals. There is good experimental work which shows that atropine decreases the tendency to ventricular fibrillation. Quinidine has been recommended for that purpose. It seems to me too depressing to the myocardium for use in

such seriously defective hearts. It has also been said to produce ventricular fibrillation. I think it is rather an unsatisfactory drug.

DR. GOLD: I wonder if we could have a little more discussion of atropine in coronary disease. The report by LeRoy and Snider of Chicago in the *J. A. M. A.* of December 13, 1941, is frequently quoted. After a given degree of coronary occlusion in dogs, 75 per cent died, presumably from ventricular fibrillation. The mortality was reduced to 35 per cent in the group which received atropine in doses of 0.1 mg. per Kg., which is equivalent to about 6 mg. or $\frac{1}{10}$ gr. for a man. They then go on to advise giving a dose of 0.8 mg. or 0.013 mg. per Kg. intravenously to a man to relieve coronary spasm in association with coronary thrombosis. They refer to the doses in the dog and in man as equivalent, although in terms of body weight, the dose advised for man is only about one-eighth of that which protected the dogs. Do these results with massive doses in dogs apply to the small doses in man? I think it is one of the very common sources of error in therapeutics, that the results of animal experiments with massive doses are applied directly to small doses in humans.

DR. PARDEE: Do you think the 0.8 mg. dose of atropine is an effective dose in man?

DR. GOLD: It is not enough to block the cardiac vagus completely. In our studies we found that 2 mg. of atropine sulfate intravenously sends the ventricular rate in auricular fibrillation up as far as it will go. Larger doses send it up no further. We may then take about 0.03 mg. per Kg. as the dose of atropine which blocks the cardiac vagus in man. According to Pilcher and Sollmann's work of 1914, the susceptibility of the dog is fairly similar, about 0.03 mg. per Kg. being required to abolish the cardiac slowing response to vagal stimulation. We should have an answer to the question whether such doses in the dog would reduce

the mortality from coronary occlusion before we use the dog experiment as a basis for the routine use of atropine in man, since it is quite out of the question to give humans the large doses which were used in dogs.

DR. PARDEE: There is another aspect to atropine. You cannot use it continually in this dose of 0.8 mg. without the patient becoming very dry and uncomfortable, and so it is eliminated as a drug for use in a chronic disease like angina. I think it is an unpleasant medicine to give and I do not give it unless there is definite evidence of myocardial irritability.

DR. GOLD: I should say that these very large doses of atropine amounting to about 3 or 4 mg. per day not only make them uncomfortable but quite wretched, and cause extreme dryness of the mouth and skin, absence of sweating, blurring of vision, weakness of the bladder with disturbance of urination, and sometimes confusion and delirium. The proof of its value should be better than it is before I would be inclined to add these burdens to the patient ill with a coronary thrombosis.

Do you give it, Dr. Eggleston?

DR. EGGLESTON: Very little. I sometimes use papaverine when signs of cardiac arrhythmia appear.

DR. GOLD: Papaverine is another drug which needs to be examined critically. Katz and his associates, of the Michael Reese Hospital, revived this drug and have given it quite a boost in their reports since 1941. They found it highly effective against the anginal syndrome in oral doses of $1\frac{1}{2}$ gr. 3 times daily. They also found it effective in controlling premature beats in oral doses up to 3 gr. 4 or 5 times a day, and a similar result in premature beats after 1 to $1\frac{1}{2}$ gr. intravenously, this lasting, however, only two to ten minutes. Papaverine possesses many of the actions of quinidine, with which it has some chemical kinship, both having

the quinoline nucleus. Like quinidine in animals, it diminishes the irritability and conductivity of the heart, prolongs refractory time, may cause A-V and intraventricular block, cardiac arrest, premature beats, coupling, ventricular tachycardia and fibrillation, and may prevent ventricular fibrillation resulting from cardiac stimulation. Papaverine relaxes blood vessels, increases coronary flow and produces a sedative action on the brain. Among the reasons why these authors prefer it to quinidine are its "powerful long-lasting direct coronary dilator action;" . . . "it may be given intravenously in large doses with a wide margin of safety;" . . . "it does not cause the toxic signs sometimes resulting from quinidine;" . . . "it is not a myocardial depressant."

It is easy to be carried away by such statements of advantages, and I know that many have been and are using it as freely as a totally innocuous drug. I have found it of equivocal value to control the pain of angina of effort in oral doses of $1\frac{1}{2}$ gr. 3 times daily. The experimental literature showing the wide variety of toxic effects on the heart, the high concentrations necessary to dilate coronary vessels and the brief duration of these effects give me very little encouragement. In one group of heart perfusion experiments in the dog the increased coronary flow lasted only seven to sixty minutes with an average of twenty-one minutes, and the smallest dose was equivalent to an intravenous injection of 5 Gm. (45 gr.) in man, which, of course, one could never give. In the May, 1940, issue of the *American Heart Journal*, Essex and collaborators reported a marked increase in coronary blood flow in the trained dog after about 1.25 to 1.75 mg. of papaverine per Kg. intravenously. That is in the range of human intravenous dosage, but the effect only lasted two to three minutes. In this connection it has also been shown in the

dog, that a dose as small as the equivalent of about 3 gr. intravenously for man, may cause a 40 mm. fall of the blood pressure. I wonder how safe that would be in the patient with coronary thrombosis. We should also note that to control ventricular fibrillation in the intact dog fairly large doses were used, and the concentrations found necessary in heart perfusion experiments were equivalent to about 15 Gm. of papaverine in the blood of a man. As to the "wide margin of safety," I should call your attention to the fact that toxic rhythms have been reported from papaverine after doses well within the therapeutic range, namely, premature beats and coupled rhythm, and ventricular tachycardia, after an intravenous injection of 1 gr., and partial A-V block after $1\frac{1}{2}$ gr. An oral dose of 3 gr. several times daily may cause sufficient drowsiness to require interruption.

I have an idea that papaverine has some value in coronary disease. How much, has yet to be established. Whether it is superior to quinidine has also to be established. Papaverine does not appear to possess the power to control auricular fibrillation. It certainly is not free of dangers.

I think it is worth while noting that in this conference very few drugs have been recommended for the treatment of angina of effort. Dr. Stewart last week referred to the controlled study of Riseman. I have here a group of papers by Riseman and associates of Boston, which indicate a dozen or more drugs as quite effective. One would judge that there was room for a good deal of choosing among drugs for the control of the cardiac pain. That is not in accord with my experience. Here is a paper in the July, 1937, issue of the *Archives of Internal Medicine*, which shows that nitroglycerin provided improvement in about 60 per cent of the patients, quinidine sulfate in about 40 per cent, aminophylline in about 35 per cent, codeine sulfate in about 30 per cent, atro-

pine in about 25 per cent and theophylline-calcium salicylate in 23 per cent.

DR. PARDEE: What is meant by improvement, Dr. Gold?

DR. GOLD: In this case, he means an increase in the capacity to walk the "two-step" before pain appears. It is not a statement of how much increase, but what proportion of patients show some improved capacity.

I would like to ask Dr. Pardee if he would be willing to comment on this list of drugs for the control of angina of effort.

DR. PARDEE: What is the rest of that list?

DR. GOLD: It shows that 22 per cent of the patients improved with erythrol tetranitrate, 14 per cent with phenobarbital, 15 per cent with digitalis, 8 per cent with sodium nitrite and about 8 per cent with dinitrophenol. I might add that in the October 28, 1943, issue of the *New England Journal of Medicine*, Riseman classified potassium iodide in 1 Gm. enteric-coated tablets as markedly effective, and the same drug in similar doses in the form of a saturated solution as ineffectual.

DR. CHARLES H. WHEELER: Did they try a placebo?

DR. GOLD: Yes, they state they tried placebos and found that lactose did not bring about improvement by the "two-step" test. But when the patients' judgment of their state was used as a criterion, about 60 per cent of them stated that the lactose placebo made them better, and the figure for incidence of improvement was reduced to about 20 per cent in the case of lactose when a third criterion was used, namely, the number of attacks of pain in a period before and during the use of the placebo.

You see, they analyzed the improvement in three ways. One was in effect to ask the patient, "Do you think you were better or did the medicine help you?" The other was to ask, "How many attacks did you have?" The third was to have him exercise on the

"two-step" until there was pain. The three groups of answers did not match. They implied that the "two-step" test gave the most reliable results, and that the patients' own judgment of the value of the medicine was such an insensitive method that patients could not distinguish one drug from another, or as they put it: "The patient's estimation of therapeutic benefit indicated that all the drugs were approximately equal in value." Their chart, as you see, does not quite substantiate that statement; the incidence of improvement, according to the patients' evaluation, varied all the way from 25 per cent for nitroglycerin to 70 per cent for codeine. On the basis of the "two-step" test, the authors concluded that "one-half of the patients were benefitted by either aminophylline or quinidine sulfate," that codeine sulfate "rarely" enabled the patient to do more work before pain developed, and that atropine was "often of value." Again, these seem to be out of line with the data. They show about 40 per cent of patients were benefitted by quinidine, about 35 per cent by aminophylline, 26 per cent by codeine and 24 per cent by atropine. Are these differences significant? There is one of the defects in such studies from the scientific standpoint, namely, that they fail to determine the precision of the method. Since there are well known spontaneous variations in exercise tolerance in patients with coronary disease, and their own results show variations as wide as 100 per cent or more, it is necessary to determine how great they are, how frequently they occur, and how far off they throw such figures as we have quoted, which presume to show one drug more effective than another. If we read only the conclusions, the answers seem decisive; if we analyze the data carefully, we become very uncertain as to how matters stand.

Dr. Pardee, do you prescribe quinidine for the angina of effort?

DR. PARDEE: Since reading these reports,

I have tried it. I have used quinidine in patients who did not seem to respond to anything else and so are the toughest patients on whom to try a new drug. I have not been impressed by its value.

DR. GOLD: Have you had any experience with that, Dr. Eggleston?

DR. EGGLESTON: No, virtually none.

DR. GOLD: Has anyone else?

DR. EGGLESTON: I never saw any logic in its use.

DR. PARDEE: Could we refer back to nitroglycerin for a moment? I do not understand the statement that patients are not improved by nitroglycerin. I think that must be dependent upon the definition of improvement.

DR. GOLD: Here was a group of about twenty patients in this report, who were given nitroglycerin to take at certain intervals during the week.

DR. PARDEE: How many times a day?

DR. GOLD: Some of them took it as frequently as every hour. At the end of this experience approximately 25 per cent of the patients judged the nitroglycerin to have helped them.

DR. PARDEE: I have used it that way at the suggestion of Roy Scott of Cleveland, who told me that he thought it was a very valuable method. It has not proved so in my experience.

DR. EGGLESTON: I, too, have employed it that way without conviction as to satisfactory results.

DR. GOLD: I know of patients with extremely frequent attacks of pain so that they were almost completely incapacitated, their pain recurring even at rest, in whom life became distinctly more tolerable with the dose of nitroglycerin under the tongue every hour.

In regard to the use of nitroglycerin I should like to stress the need for attention to dosage. I do not believe I have ever seen a patient requiring a dose to relieve the

heart pain, which is so large as to cause disturbing head symptoms. So many patients carry on with nitroglycerin in doses which nearly blow off their heads. They hesitate to take it frequently enough because of it. From the standpoint of relief of pain, they get on just as well when the dose is reduced below the threshold of head symptoms. I am also impressed with the need for urging patients to take nitroglycerin more rather than less frequently. They often fear habit or poisoning by it, and I am inclined to believe that physicians do not do enough to dispel those fears. There is no danger of either in proper therapeutic doses.

Dr. Eggleston, what do you do for the patient with coronary disease who is having attacks of pain at rest? How do you manage a person of that kind?

DR. EGGLESTON: This is the management of a patient with the decubital form of angina?

DR. GOLD: Yes.

DR. EGGLESTON: It has been my practice to attempt to find out whether there are any emotional, digestive or other factors which might have been responsible for precipitating these attacks of angina. If there are, I try to eliminate those as effectively as I can. Sometimes, sedatives in sizable doses will protect such a patient against decubital angina. Aside from that, the usual remedies are given in the hope that they will relieve the patient, and if they fail, then nitroglycerin. The value of nitroglycerin is to be judged in terms of the relief of the attack, and not in terms of continuous use during the day. It may also be used for the prevention of an attack. If the attack occurs at rather fixed intervals, the drug sometimes is very beneficial, and will tide these patients through. Usually there is some psychic disturbance in the form of dreams, or something similar to that which may or may not be unearthed on careful questioning of the patient, which seems to be responsible. I for-

got to mention the rôle of the overdistended bladder. That occasionally seems to precipitate attacks. If the attacks then continue and are not relieved by the usual range of agents which you discussed here, many of which I do not use, I consider the desirability of a surgical approach for the relief of the angina, either by paravertebral block, which I do not particularly favor, or preferably by rhizotomy.

DR. GOLD: Is that what you do, Dr. Pardee?

DR. PARDEE: In patients with coronary pain at rest and at night, one might suspect a slow occlusion. We should examine the electrocardiogram and perhaps do a sedimentation test to rule out that factor. Having ruled that out, I approach it very much as Dr. Eggleston has outlined. In most of these patients, I think there is overactivity of the nervous mechanism causing spasm. Sedatives have been very successful in a number of cases. After large doses of phenobarbital, which keep them semi-stuporous for three or four days, they sometimes have much less pain when they come out of the depression. In a few cases this has marked the beginning of a conspicuous improvement. Nitroglycerin does not relieve most of these attacks. You ask them how long the attack lasted after the dose and they say "ten minutes." I think such a long period shows that the nitroglycerin was not responsible for the relief.

There is one drug, erythrol tetranitrate, which often helps the nocturnal attacks. A tablet of 30 to 60 mg. ($\frac{1}{2}$ to 1 gr.) seems to carry them through the better part of the night, and if they wake up in the middle of the night they can take a second one. I have not found mannitol hexanitrate as effective.

DR. GOLD: I should like to ask a question in relation to the large doses of sedatives. Do you ever find that large doses of sedatives make patients worse? They still awaken at

night with pain, and the pain is now much more severe. Before using the sedative, a mild pain would awaken the patient, and shortly after sitting up the pain subsided. Apparently, the pain in these cases is associated with the recumbent position. Under the influence of a large dose of a sedative, stronger stimulation is necessary to awaken them; and when they do awaken, the pain is excruciating. Such cases are not frequent but I have seen a few. It looks like intense sedation may be a double-edged sword.

Have you ever encountered that?

DR. PARDEE: No.

DR. EGGLESTON: I have not seen that.

DR. WHEELER: I think that surgery is the best bet for patients who are subject to severe attacks of cardiac pain at rest.

I should also like to mention that in patients with severe nocturnal pain and little or none during the day, hiatus hernia may be the cause. I have seen four or five such patients, and three of them had hiatus hernia.

DR. WALTER MODELL: I want to say that we had some experience with a few patients with just that type of symptomatology, who were relieved by the use of mercurial diuretics. I wonder if you could explain such a thing?

DR. EGGLESTON: I have seen a few of them benefitted by the mercurials.

DR. GOLD: I should like to stress the value of dehydration as a means of controlling cardiac pain which occurs at rest, and especially for those attacks which occur while the patient is resting in the recumbent position, nocturnal attacks of pain. Not all such patients respond, but some do in a dramatic way. I have the impression that the pain in those patients who also have exertional dyspnea or nocturnal dyspnea is more apt to respond well. Because of a clearcut relationship between the relief of the dyspnea and the pain by dehydration in some cases who have both symptoms, I

am inclined to think that in some cases cardiac pain is the sole clinical manifestation of left heart failure. If you treat them as cases of left heart failure, their capacity for exertion without pain is enhanced and nocturnal pain may either lessen or vanish.

DR. EGGLESTON: Are not those the same patients in your experience who are benefitted by digitalis?

DR. GOLD: As a rule digitalis does not help them. Their symptoms improve when they lose several pounds of extracellular fluid, as the result of a milk diet which greatly restricts the salt intake, water ad lib, and a daily dose of a mercurial. Some of these patients are freed of nocturnal attacks of pain for two or three days after the dose of mercurial, and as the water is regained by the end of the week, the pain returns. A proper dosage regimen for maintenance has to be established. However, they have no manifestations of failure with congestion in the usual sense.

DR. EGGLESTON: Have you ever tried that without the mercurial?

DR. GOLD: I do not believe I have, but I should not be surprised, if satisfactory results were at times obtained without it, for salt restriction alone often brings about considerable dehydration.

DR. CATTELL: I think we would like to hear about the surgical treatment of coronary artery disease.

DR. BRONSON RAY: In general, there are three useful surgical procedures and these are all based on what we understand to be the anatomical arrangement of the innervation to and from the heart.

There are visceral afferent fibers from the heart, through the middle cardiac nerve to the middle cervical ganglion, through the inferior cardiac nerve to the inferior cervical ganglion, and by rami from the first to the fifth thoracic ganglia of the thoracic sympathetic chain. Visceral afferent fibers which transmit pain impulses are not called sym-

pathetic fibers. These afferent fibers pass through the ganglionated chain, and enter the cord via the posterior nerve roots. They have their cells of origin in the posterior ganglion, just as somatic afferent fibers do, and enter the cord to cross and ascend in the spinal thalamic tract. We believe that all pain impulses coming from the heart, regardless of what nerves they travel, enter the cord between the first and fifth thoracic segments. The innervation is, of course, bilateral.

Following the stimulus of the visit of Royal and Hunter to this country some years ago, stellate ganglionectomies were employed for a number of conditions, among them, anginal pain. In general, the operation included the inferior cervical and the first thoracic ganglia. In a number of patients this relieved the pain but in a greater number of others it failed. It was not until we began to try to formulate the anatomy of pain referred from the heart that the explanation was forthcoming. It is obvious that if, in a given case, the major portion of pain coming from the heart takes a course through nerves which traverse the stellate ganglion, the removal of that ganglion will stop the pain; but if some of the pain or all of the pain is mediated through other fibers, stellate ganglionectomy is a half-way measure or no measure at all.

The three procedures in vogue all consist of interrupting these afferent pathways either in the sympathetics or in the posterior roots. One procedure is the multiple injection of alcohol in the paravertebral region to destroy, by alcohol, the four or five upper ganglia of the thoracic ganglionated chain. Usually, the injection is made only into the first four, ignoring the fifth, because four needles are bad enough, and five are that much worse. To introduce a needle to the necessary depth (about 7 cm.) in the back is no mean procedure. It is a blind procedure at best and one must trust that his luck and

skill together will get at least several of the needles near where he wants them. Then the alcohol is injected with the hope that it will destroy just the right nerves. Often enough, alcohol injection is successful in eliminating the pain but it has serious disadvantages which must be taken into consideration. These, I believe, can be listed as follows: There may be failure because it is a blind procedure. In a very high percentage, at least 30 per cent in my experience, there is painful radiculitis following this procedure as a consequence of alcohol acting on the intercostal nerves. This is not to be belittled because some patients who have been relieved of the angina would gladly exchange the one for the other after experiencing the radiculitis from alcohol. In one patient of mine radiculitis lasted for at least six months. I think his physician has never again considered an alcohol injection for such a case. Fortunately, however, other patients have had much happier results. That the alcohol or needle may enter the pleura causing pleurisy and even pneumonia is a recognized complication of the procedure. A more serious complication, and a few of these cases have been reported in the literature, is that the needle may somehow enter the subarachnoid space. The subarachnoid space comes out as a sheath along the nerve roots quite a distance sometimes. It is possible, when a needle is improperly placed, to inject alcohol into the subarachnoid space producing complete myelitis which has been permanent in some instances. There is the objection of recurrences of pain when the effects of the alcohol wear off. There is also the objection that, if the pain is bilateral or primarily substernal, the injections have to be made on both sides to be effective.

Another procedure is to resect the sympathetic chain, thereby interrupting the visceral afferent fibers going to the cord. At the same time, of course, the sympa-

thetic fibers are interrupted. A few years ago an article appeared in the *J. A. M. A.* in which the claim was made that this operation benefitted the circulation of the heart, because as the result of the removal of part of the sympathetic chain, dilatation of the coronary vessels could be expected. There was no proof for that, and such experimental information as we have would indicate that the reverse is probably true, that is, when the heart is sympathectomized, the coronary arteries appear to contract rather than to dilate. This is in contrast to what happens in the peripheral vasculatory system, in the hands, for example. So, whatever benefits accrue from the sympathectomy result from the interruption of afferent nerves carrying the pain.

The third operative procedure consists in cutting the first four or five posterior roots through a laminectomy. We are not sure how much of a rôle the fifth plays, and sometimes it is not convenient to cut more than four. We have had experience with this operation in eleven patients, with the sympathectomy in six patients, and I do not recall how many we have injected with alcohol, but the number is not large. I believe that there are certain advantages in the rhizotomy, the chief one being that, if the pain is bilateral, it is just as easy to cut the roots on both sides as on one, and thus a bilateral operation can be completed at one sitting. A sympathectomy on one side is just about as hazardous as a laminectomy and rhizotomy. I believe the choice of the operation needs to be suited to the case, and depends on whether the pain is unilateral or bilateral. There are also these points for consideration when deciding between the two operations. Horner's syndrome follows sympathectomy and is a disadvantage; it does not occur with rhizotomy. However, following rhizotomy there will be some sensory loss in the upper thoracic dermatomes, which is not serious, but nonethe-

less would be desirable to avoid if possible. There need be no demonstrable sensory loss after sympathetic resection.

Of the eleven patients with rhizotomy, one died on the second day postoperatively, of a recurrence of coronary occlusion. Another patient died three weeks after his operation when he was up and around the ward and presumably progressing satisfactorily. This was his first coronary occlusion. One patient was lost track of, but for the two months that we observed the patient after operation the result was satisfactory in that the pain was relieved and the patient felt gratified with the result. Two patients died two and three years, respectively, after operation. That leaves six patients that we now have under observation. One who was disabled for about ten years with his angina, following bilateral rhizotomy became head of a USO center in Connecticut. It is now nearly three years since his operation, but I am impelled to report that in the last six months he has again become incapacitated, has had what we believe to be a series of coronary occlusions, and has enough discomfort in his thoracic region to cause him a great deal of trouble.

Another patient who has been of great interest also, had angina for about eight years. He had a very unfortunate experience with an attempt at paravertebral block, and was miserable with neuritis from irritative effects of the alcohol. Both the neuritis and the angina were relieved by rhizotomy. This man, a physician, leads a life that would, I think, make almost any of us tired by midday. Another is a patient I do not feel very happy about. He is one of the clinic patients who was known to be a chronic complainer. Unfortunately, during the postoperative period of immobilization of the shoulder girdle he developed painful peri-arthritis and it, rather than the former angina, has become his chief source of discomfort. Therefore, the results, perhaps,

are not entirely satisfactory. The patients are not rehabilitated completely and there are disadvantages to almost any method. But from the standpoint of rational procedure in properly chosen cases I think that it has value.

There is reason to believe that there may be some other pathways for sensation from the heart. The patients who lose their pain by some operative procedure or other will get a warning of discomfort in the chest when they overexert themselves. It is nothing like their old pain, but it is a warning, and in two patients there has been the development after these operations of dull pain in the jaw region on both sides. The jaw pain does not come on nearly as frequently as the former angina pain did, and it is not disabling; it does not slow them up very much. The pathway or mechanism for that pain is a mystery.

DR. MODELL: Dr. Ray, in those patients who had coronary occlusion was there any pain during the attack?

DR. RAY: Yes, they had pain in the chest. It was different in degree and they recognized it as being somehow different in quality from any pain that they had had before.

DR. PARDEE: I remember one of those cases, a woman, who had coronary occlusion, and who died in the ward. In her final attack she had pain radiating from the right arm down to the hand.

DR. RAY: You might be interested in the review of the case of this girl who is being brought in on her bed. She is thirty-six years of age. She had angina for four years. Her mother and father both expired in the early fifties or thereabouts, with vascular disease, and one brother made a sudden exitus from coronary disease at the age of thirty-eight. Dr. Harold Stewart has examined this girl. Her pain occurred after exertion but it also often came at night and it also came when she was sitting still.

Anxiety was rather the most consistent producer of her pain. The standard exercise tests left no room for doubting the diagnosis but she was thoroughly investigated for a possible diaphragmatic hernia. It is now five days postoperative; she had the sympathetics resected including the stellate and first five thoracic ganglia, and the chain in between. The left upper extremity shows all the effects of sympathectomy. It is warm and dry while the other is cool and moist. She also has a Horner's syndrome. She still has some discomfort in the operative wound, but she has had no angina to date, and she had not gone a day without it prior to the operation for four years even though she had spent some periods of time in bed.

How do you feel?

PATIENT: Fine!

DR. RAY: Do you think you would have had some pain by now?

PATIENT: I think I would have it right now in front of all these people.

DR. RAY: When she consulted me first she had two attacks in rapid succession. This is also interesting about her: She had not relied much on nitroglycerin because her attacks were short and the nitroglycerin gave her an uncomfortable feeling, particularly palpitation. She felt that taking the nitroglycerin really did not shorten the individual attack enough to warrant the discomfort of palpitation.

DR. GOLD: Was this a one-sided operation?

DR. RAY: The pain and the operation were left-sided. If pain had been bilateral I think I would have considered a bilateral rhizotomy through a laminectomy.

DR. GOLD: I think our time is up.

SUMMARY

DR. GOLD: You will recall that in our first conference on this subject consideration was given to the general features of the treatment of the various clinical types of

coronary artery disease. There was some discussion of the treatment of shock with clyses, infusions of glucose and of plasma, the use of the xanthines like theobromine and sodium acetate, and aminophylline, and the use and dangers of digitalis in heart failure associated with coronary thrombosis.

The subject was extended today to include the question of bed rest in coronary thrombosis, morphine and the other opiates, sedatives, demerol, nitroglycerin, quinidine, papaverine, atropine, the mercurial diuretics and the surgical measures in the management of coronary artery disease.

Special attention was paid to the need for critical reading of the literature on the drugs used in coronary artery disease, and it was pointed out that the evidence for the value of most of them leaves much to be desired. The extraordinary spontaneous variations in the course of the susceptibility to pain in patients with coronary artery disease is a

source of error in the judgment of the value of drugs, and this appears to be largely responsible for the differences in views regarding the value of drug therapy in this disease. Animal experiments are often misleading in that the results with massive doses may have no bearing on the use of these agents in the smaller therapeutic doses in man. Special attention was paid to the literature on atropine and papaverine. There seems to be considerable doubt regarding the utility of these agents in the dosage range which can be safely administered to man. Attention was called to the value of dehydration with salt restriction and the organic mercurials for the treatment of the patient subject to attacks of cardiac pain at rest or nocturnal attacks of pain. Several types of surgical procedures were described having as their purpose the interruption of the pain pathways from the heart, paravertebral alcohol injections, sympathectomy and rhizotomy.

Clinico-pathological Conference

Purpura, Arthritis, Hepatomegaly and Hepatic Failure*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, B. T., a thirty-five year old dentist, entered the Barnes Hospital for the first time complaining of chills, fever and general malaise. The family history was significant in that the patient's father had diabetes and had had a stroke. Several members of his father's family died from the complications of hypertension. The past history revealed that at the age of ten the patient had an episode of jaundice. At eighteen he developed pneumonia and pleurisy, and following this illness, a diagnosis of pulmonary tuberculosis was considered and the patient was sent to Colorado for four months; he recovered completely. For some years the patient had attacks of acute pain in the upper abdomen which usually followed rich or fatty meals and lasted fifteen to twenty minutes. His stools had always tended to be loose, and six years prior to entry, at the time of an attack of abdominal pain, questionably tarry stools were noted. During the three successive summers preceding his first admission, the patient had attacks of malaria for which he took atabrine and quinine. One year before entry, he had mild cystitis which was apparently self-limited. He had never used alcohol to excess.

Two days prior to admission, the patient awakened with a chill, his temperature was

found to be 102°F., and he complained of general malaise. The following day, although he had no more chills, the fever persisted, and he entered the Barnes Hospital on May 18, 1939.

On physical examination, the patient's temperature was 40°C., pulse 155, respirations 30, and blood pressure 120/88. He was moderately obese and appeared acutely ill. The pupils reacted normally. The sclerae were not icteric. The upper respiratory tract was normal and the lungs were clear. The heart was normal in size; the rhythm was regular, the rate rapid, and there were no murmurs. The liver edge was felt 8 cm. below the right costal margin. It was smooth, firm, slightly rounded and non-tender. The spleen was not palpable.

The laboratory findings on entry were as follows: Blood count: red cells, 4,290,000; hemoglobin, 86 per cent; white cells, 7,200; differential count; "stab" forms, 29 per cent; segmented forms, 43 per cent; lymphocytes, 24 per cent; monocytes, 4 per cent. Blood smears revealed no malarial parasites. Urinalysis: negative. Blood culture: no growth. Kahn reaction: negative. Blood chemistry: sugar, 127 mg. per cent; non-protein nitrogen, 22 mg. per cent. Agglutination tests: B. typhosus 4+, 1:80, 2+, 1:160, negative, 1:320; brucella, negative.

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† By Robert J. Glaser, M.D.

The patient was treated with quinine and his temperature became normal. A diagnosis of probable malaria was made and he was discharged on May 21, 1939.

After leaving the hospital, he continued to take quinine and felt well until one month before his second admission when he developed "boils." Although at one time he had as many as twenty, they all healed without treatment. One week later, he began to have pains in the knees, ankles, hips, elbows and wrists and some of the joints became swollen. The process was migratory but persistent, and the patient returned to the hospital for the second time on February 26, 1940.

The physical examination was unchanged except that there was slight swelling and tenderness of the ankles and wrists.

The laboratory studies revealed the blood count to be within normal limits. The corrected sedimentation rate was 1.5 mm. per minute. The blood sugar and non-protein nitrogen were normal. The blood cholesterol was 263 mg. per cent. An electrocardiogram was normal.

During his brief stay, the patient's temperature remained within normal limits. He was discharged on February 29, 1940, with a diagnosis of atrophic arthritis and hepatomegaly of unknown origin.

Following discharge, the patient's joint manifestations gradually subsided, and he was well enough to gain acceptance into the Army. After two years of service during which he worked hard, the patient again began to have intermittent episodes of swelling and pain in many of his joints, associated with purpuric spots on the lower legs. He entered an Army hospital where a diagnosis of infectious mononucleosis was made. While in the hospital the joint symptoms and purpura persisted. They recurred intermittently after he left the hospital and six months later, the patient re-entered an Army hospital for study. Liver function

studies, done because of the hepatomegaly, were found to be normal. The gallbladder was not visualized on repeated cholecystograms. The patient was discharged without any diagnosis having been made.

The arthritis and purpura continued to occur intermittently. After an eleven-month interval, the patient was advised to re-enter the hospital for cholecystectomy although, at that time, he had no complaints referable to the biliary tract. At operation the gallbladder was found to be normal but the appendix, which was described as being acutely inflamed, was removed. A liver biopsy was reported as showing "hepatitis." Following the operation, the patient developed atelectasis of the left upper lobe of the lung, associated with cough and fever, which cleared in one week. Following discharge from the Army hospital, he continued to have arthritis and purpura of increasing severity. A high protein, high carbohydrate, high vitamin diet was given without apparent favorable effect. On two occasions the patient had sudden pain in the left upper anterior chest, associated with a non-productive cough and fever. Dyspnea on exertion gradually developed, as did ankle edema following moderate activity. One month before the third Barnes Hospital entry, slight bleeding from the nose, mouth and rectum was noted. Repeated examinations of the blood revealed the bleeding time, clotting time and prothrombin time to be normal, but the corrected sedimentation rate was persistently elevated. A low grade fever recurred periodically and the patient lost 30 pounds during the seven months following his discharge from the Army hospital. He returned to the Barnes Hospital for further study on December 11, 1945.

On entry the temperature was 36.8°C., pulse 100, respirations 16, and blood pressure 110/80. The patient appeared well developed and well nourished and was in no distress. Extensive purpura was noted on

both lower extremities, particularly over the legs and ankles where the lesions were confluent. The eye grounds were normal. Cervical and axillary nodes were soft and moderately enlarged. Examination of the upper respiratory tract was negative. The lungs were clear throughout and the heart was normal. Examination of the abdomen revealed a long, well healed scar in the right upper quadrant. The liver was felt 6 cm. below the right costal margin; the edge was quite firm, slightly tender and somewhat irregular. The spleen was not felt. There were questionable signs of ascites. The knees and ankles were painful on motion. There was no edema.

The laboratory findings were as follows: Blood count: red cells, 4,470,000; hemoglobin, 15.9 Gm.; white cells, 8,100; differential count, within normal limits; platelets, normal. Urinalysis: negative except for 4⁺ urobilin. Stool examination: negative. Quantitative Kahn reaction: 4 units. Blood chemistry: non-protein nitrogen, 11 mg. per cent; total proteins, 9.6 Gm. per cent; albumin, 2.3 Gm. per cent; globulin, 7.3 per cent. Icteric index: 30. Bromsulfalein test: 40 per cent dye retention in 30 minutes, 30 per cent in 40 minutes. Cephalin-cholesterol flocculation test: 4⁺. Hippuric acid test: 59 per cent excretion. Van den Bergh test: direct, 2.7 mg. per cent; indirect, 4.3 mg. per cent. D/I ratio: 62 per cent. Blood vitamin C level, 2.1 mg. per cent. Prothrombin time: 92.5 per cent of normal. Rumpel-Leede test: negative. Electrocardiogram: normal.

The purpura and joint pains persisted. The patient was placed on a diet devoid of milk, eggs and wheat; results were indifferent in that the cyclical character of the illness continued. Repeated Kahn tests were reported as doubtful. The patient developed increasing abdominal fluid. One month after admission, acute inflammation of the right eardrum was noted and penicillin

therapy was instituted. The tympanic membrane was incised and purulent exudate was evacuated; on culture, alpha hemolytic streptococci were grown from the pus. An abdominal paracentesis was performed and 6,750 cc. of slightly cloudy, straw-colored fluid were removed. The specific gravity of the specimen was 1.006, and the total protein 1.4 mg. per cent. No tumor cells were identified on microscopic examination of sections of the centrifuged sediment. Following paracentesis the patient felt much improved, and at his own request, was allowed to return to his home. Slight nose bleeds and occasional melena were noted in the hospital, and low grade fever was present from time to time. At the time of discharge on February 15, 1946, the red cell count had fallen to 3,310,000 and the hemoglobin to 12.3 Gm. The icteric index was 30 and the total proteins 7.6 Gm. per cent. The patient was advised to follow a high protein, high carbohydrate, and low fat diet; vitamins, skimmed milk, and choline chloride were prescribed in large doses.

While at home, the patient developed a very good appetite, gained weight, and regained a feeling of well being. However, the reaccumulation of fluid in his abdomen again made him so uncomfortable that he was unable to eat and he re-entered the Barnes Hospital for the fourth and last time on February 22, 1946, for paracentesis.

The significant findings on physical examination included icterus, a markedly protuberant abdomen and purpura extending from the ankles to the thighs. No joint involvement was apparent.

The laboratory data were as follows: Blood count: red cells, 3,370,000; hemoglobin, 10.3 Gm.; white cells, 6,100; differential count, within normal limits; platelets, normal. Urinalysis: negative. Stool examination: guaiac positive. Blood chemistry: non-protein nitrogen, 16 mg. per cent; cephalin-cholesterol flocculation test, 4⁺;

total proteins, 7.1 Gm. per cent; albumin, 2.3 Gm. per cent; globulin, 4.8 Gm. per cent. Blood Wassermann reaction: positive.

A paracentesis was done and 3,250 cc. of slightly cloudy amber fluid, similar to that obtained on the previous admission, were removed from the abdomen. A Talma omentopexy had been advised by the physician who followed the patient at his home. At the patient's insistence, and despite the marked degree of liver damage, his request for operation was granted, and a laparotomy was performed; 500 cc. of straw-colored fluid were evacuated. The spleen was noted to be enlarged from two to three times its normal size. The stomach, duodenum and pancreas seemed normal. The size of the portal veins could not be determined because of adhesions from the previous laparotomy but the liver was small and nodular. The left lobe was biopsied, and omentopexy was performed. Microscopic examination of the biopsy specimen was reported as showing "portal cirrhosis."

Thirty-six hours after the operation, the patient complained of shortness of breath. His respirations gradually became slow, deep and irregular, and his pulse rate rose. The patient became increasingly drowsy, gradually lost consciousness and died quietly. During the last three days of life, his temperature, which had been normal, rose to 38°C.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This is a very unusual case, presenting many interesting features. In discussing it, we can consider two separate aspects; first, the purpura and the associated arthritis, and second, the hepatic disease. Subsequently, they can perhaps be correlated. Dr. Reinhard, how would you classify the extensive purpura?

DR. EDWARD H. REINHARD: The results of the studies on the coagulation mechanism were normal. Therefore, I would explain

the purpura on the basis of abnormal capillary permeability.

DR. ALEXANDER: Is not all purpura due to abnormal capillary permeability?

DR. REINHARD: In the sense that the blood must pass through the capillary wall, yes; often, however, the defect is primarily in the blood coagulation mechanism.

DR. ALEXANDER: Dr. Moore, if there is a defect in the blood coagulation mechanism, is there not also a defect in the capillary wall?

DR. CARL V. MOORE: Not necessarily. The classical example is in hemophilia, in which, although there is a defect in coagulation, purpura is extremely rare.

DR. ALEXANDER: The Rumpel-Leede test, which is usually positive in thrombocytopenic purpura, was negative here. Further, this man did not bruise easily. Are there any suggestions as to a diagnosis?

DR. REINHARD: There are certain features in this case which suggest a diagnosis of Henoch-Schönlein purpura. The joint manifestations and abdominal pain are both consistent.

DR. ALEXANDER: Is there anything against the diagnosis?

DR. REINHARD: I do not believe that all the findings are explicable on the basis of that diagnosis alone.

DR. ALEXANDER: If the hemorrhagic phenomena are considered apart from the evidences of liver disease, are they characteristic of Henoch-Schönlein purpura?

DR. MOORE: Yes, they are.

DR. ALEXANDER: The so-called triad which comprises Henoch-Schönlein purpura or Osler's purpura includes purpura or urticaria, arthritis and abdominal pain. These can occur singly or together. This patient's first hospital admission was for abdominal pain; he entered the hospital a second time with arthritis, and on his third admission he had both arthritis and purpura. In this syndrome the capillaries may

be permeable to plasma or blood; if the former, urticaria results, and if the latter, purpura. Indeed, hemorrhagic urticaria can be seen occasionally. Is there anything distinctive about the arthritis?

DR. REINHARD: It is cyclic and clears without residual; in these respects, it resembles the arthritis of rheumatic fever.

DR. ALEXANDER: Do you believe that the arthritis of Henoch-Schönlein purpura and that of rheumatic fever are indistinguishable?

DR. REINHARD: In rheumatic fever the joints are usually hot and red; in Henoch-Schönlein purpura they usually are not.

DR. ALEXANDER: Are there any other diseases in which arthritis, fever and purpura occur?

DR. W. BARRY WOOD, JR.: If urticaria is included, then serum sickness and drug allergies such as those seen with penicillin or the sulfonamides can be added.

DR. ROBERT J. GLASER: Meningococcemia also enters into the differential diagnosis.

DR. ALEXANDER: Yes. Rocky Mountain Spotted Fever as well as certain other infectious diseases must likewise be mentioned. Dr. Wade, this patient had a very high serum globulin. His total protein was 9.6 Gm. per cent with a globulin fraction of 7.3 Gm. per cent. What is your interpretation of these findings with respect to this case?

DR. LEO J. WADE: When the total proteins are increased, the increase is usually in the globulin fraction. Such increases in globulin can occur in such diseases as rheumatic fever, tuberculosis and pneumonia, but they are uncommon. More commonly, increases of this degree are seen in multiple myeloma, lymphopathia venereum, Boeck's sarcoid or lupus erythematosus.

DR. ALEXANDER: Arthralgia, fever and purpura are seen in lupus erythematosus not uncommonly. The skin lesions of lupus,

in its later stages, can be purpuric. Is there any other disease in which fever, purpura, arthralgia and a high serum globulin are common?

DR. WOOD: They occur in periarteritis nodosa.

DR. ALEXANDER: That is correct. I would also add dermatomyositis. Some of the manifestations are reversible, particularly the arthritis, the purpura and the fever. In rheumatic fever, drug allergy, serum sickness and Henoch-Schönlein purpura, the patient almost always recovers from the initial attack. Attacks can occur repeatedly and yet leave no residual effects, except in the case of rheumatic fever in which irreparable heart damage is common. As to just when the changes become irreversible is a question of much interest to many investigators.

DR. WOOD: Dr. Alexander, do you believe that in this case microscopic lesions of periarteritis nodosa will be found?

DR. ALEXANDER: There is evidence that periarteritis nodosa may be the common irreversible lesion in severe rheumatic fever, serum sickness and certain forms of drug allergy. I know of no instance, however, of Henoch-Schönlein purpura in which periarteritis nodosa has been described; thus it is pure inference to say that because these other diseases eventually progress to irreversible changes, Henoch-Schönlein purpura may do likewise. As a matter of fact the number of cases of Henoch-Schönlein purpura that have come to autopsy is very small. For this reason the present case assumes great importance. I would not be surprised, however, if the lesions of periarteritis nodosa were found in this case.

This patient died of hepatic failure; his liver was noted to be enlarged on each physical examination from the time of the first admission in 1939 until his death. The only past history of significance in regard to the liver disease was that the patient had

had jaundice at the age of ten. It is very important that when he was observed in 1939, he gave a history of abdominal pain and tarry stools; from this information the inference is made that he had had purpura at that time. Dr. Wade, can the large liver and purpura be reconciled? If not, what was the cause of the hepatomegaly?

DR. WADE: In light of subsequent events, the hepatomegaly may have been merely a manifestation of an early stage of cirrhosis of the liver. I do not know of any way to relate the hepatomegaly and the purpura.

DR. ALEXANDER: As late as 1941 the patient was not very ill; he had no signs of liver disease and only the early signs of Henoch-Schönlein purpura. A biopsy specimen, taken in 1943 when the patient was in the Army, was reported as showing hepatitis. Coincidentally, the purpura became more severe and the signs and symptoms of liver disease developed. That these changes were due to the same disease is not certain, but if not, the coincidence is striking. Dr. Wade has suggested that the signs first noted may have represented the early stages of cirrhosis. Dr. Wood, would you have any other interpretation?

DR. WOOD: I think Dr. Wade's suggestion is a good one. However, the patient had an attack of jaundice at the age of ten, and the question may be raised as to whether he did not have infectious hepatitis with repeated recurrences which eventually led to Laennec's cirrhosis of the liver. In favor of such a hypothesis is the report of the biopsy taken when the patient was in the Army.

DR. WADE: I would agree that infectious hepatitis may have been the cause of the cirrhosis.

DR. MOORE: Dr. Alexander, this patient may never have actually had malaria. His chills and fever may have been merely manifestations of recurring toxic hepatitis

or infectious hepatitis—I do not know how these two could be differentiated.

DR. BRUCE KENAMORE: On the other hand, if the patient did have malaria, it may have contributed to the hepatic failure. It has been reported that chronic malaria causes liver damage.

DR. ALEXANDER: In relation to this discussion further comment should be made regarding the nature of the hepatic lesion. Both Dr. Moore and I saw slides of the specimen obtained on liver biopsy in 1943; it showed inflammation with much round cell infiltration about the liver cords, but there was, in our opinion, no evidence whatsoever of cirrhosis.

DR. ROBERT A. MOORE: The findings were not those of infectious hepatitis either.

DR. ALEXANDER: In 1943 the liver showed changes which were not those of either infectious hepatitis or cirrhosis; yet the patient died with some indications of portal obstruction which, therefore, must have developed within these two years. Dr. Wade, would relatively severe hepatitis cause such changes in a year's time? Would you expect to find a "hob-nail" liver in the final stage?

DR. WADE: From the surgeon's description at the time of the final laparotomy, it sounds as if the liver were cirrhotic. A finding which seems inconsistent with portal cirrhosis, however, is the total protein. Ordinarily, there is an increase in the globulin fraction in cirrhosis but it is a compensatory increase, and the total protein is not usually above normal. Unless the increased total protein is explained in some other way, the diagnosis of Laennec's cirrhosis seems somewhat doubtful.

DR. ALEXANDER: The high total proteins were noted only a few months before death, however.

DR. WADE: They assume less significance in that case.

DR. ALEXANDER: We must now decide whether the patient had hepatitis and pur-

pura as unrelated entities or whether conceivably the liver disease could have been a visceral manifestation of Henoch-Schönlein purpura. In view of the fact that in Henoch-Schönlein purpura the kidneys, the heart, and certainly the spleen may be effected, it is possible that the liver likewise might be involved.

DR. WOOD: Dr. Moore, would you comment further on your interpretation of the sections of the liver biopsy specimen.

DR. R. A. MOORE: I can only say that, in my opinion, this process represented a non-specific subacute hepatitis, and did not exhibit the pathologic picture of infectious or epidemic hepatitis.

DR. WOOD: Dr. Alexander, in view of the findings in the biopsy material I think the postulate that the liver disease was a manifestation of Henoch-Schönlein purpura should be entertained.

VISITING PHYSICIAN: Dr. Moore, were the blood vessels in the biopsy section abnormal in any way?

DR. R. A. MOORE: No.

DR. ALEXANDER: That is a good point. In Henoch-Schönlein purpura no structural lesion of the blood vessels is found. The permeability is increased without apparent structural damage. Are there any further comments?

DR. PALMER H. FUTCHER: Have either quinine or atabrine, which apparently this patient took on several occasions, been recorded as causing either liver disease or purpura?

DR. ALEXANDER: Dr. Moore, can you answer that question?

DR. C. V. MOORE: Not to my knowledge, but I am not thoroughly familiar with the literature.

DR. ALEXANDER: In summary, then, the concensus of opinion of this group seems to favor a single diagnosis, namely, Henoch-Schönlein purpura, to account for the purpuric, arthritic and hepatic aspects of

the patient's disease. If this case is shown to be one of Henoch-Schönlein purpura with liver damage, it will be unique in the annals of medicine, for I believe that no such case is recorded in the literature. We shall ask the pathologists to give us the final answer.

Final Clinical Diagnosis: Henoch-Schönlein purpura.

PATHOLOGIC DISCUSSION

DR. ROBERT A. MOORE: The gross findings indicated first that there was some type of cirrhosis of the liver, but it was not of the usual type for there were large, irregular trabeculae throughout the liver in which the substance was entirely destroyed. In classical portal cirrhosis the nodules of regenerating liver cells are about the same size and are equally distributed throughout the liver substance. Second, there was splenomegaly, which had no particularly characteristic gross appearance, and there was two-fold evidence of portal hypertension; namely, ascites and ruptured varices of the esophagus with abundant evidence of hemorrhage. An unexplained polyserositis was indicated by pericardial adhesions and by adhesions involving the capsule of the liver and the transverse colon.

Turning to the microscopic sections, Figure 1 is representative of one part of the liver. There is total destruction of the liver with no structures remaining except the bile ducts; the connective tissue between the bile ducts is moderately cellular but not collagenous and it is heavily infiltrated with cells. Many of these cells are lymphocytes and mononuclear cells and a very few are polymorphonuclear leukocytes. Inspissated bile within the lumen of a bile duct may be seen. In the next section (Fig. 2), an area of regeneration is shown. There are large liver cells, many of them multinucleated, in association with the increased

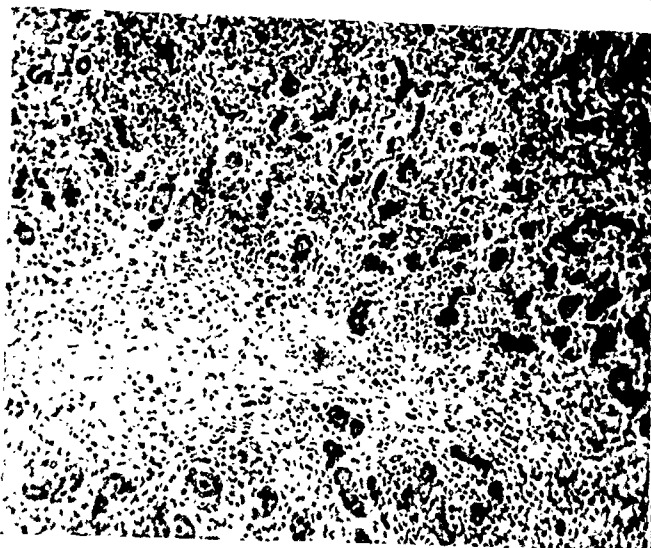


FIG. 1. Low power view of a section of the liver showing destruction of the parenchyma. Note the bile ducts with inspissated bile. x. 47.

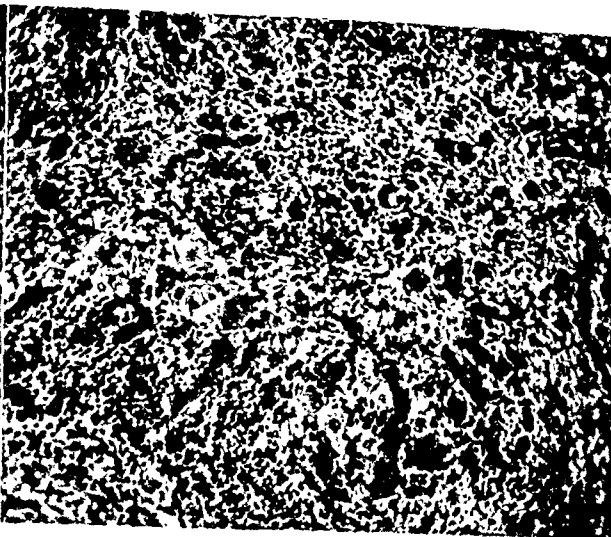


FIG. 2. Lower power view of a section of the liver showing areas of regeneration. Many of the liver cells are multinucleated and there is a heavy cellular infiltration. x 47.

fibrous tissue and the heavy mononuclear cellular infiltration seen in Figure 1. There was little evidence of actual necrosis of hepatic cells in any of the liver sections that we examined. The liver was regenerating; it had withstood the injury which was of

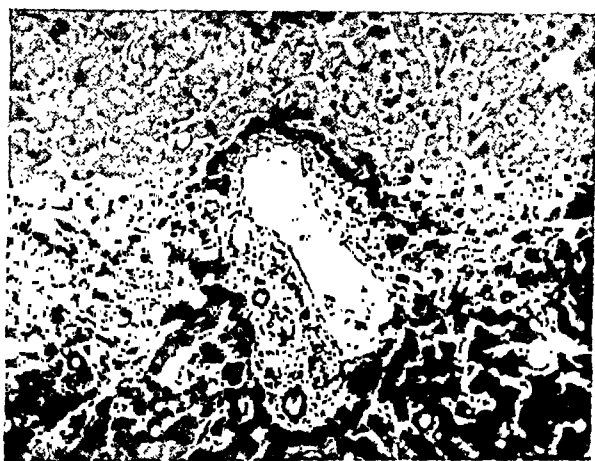


FIG. 3. Low power view of a section of the liver which shows essentially normal structure. Compare this section with those in Figures 1 and 2. x 47.

such a character that it had led to considerable cellular infiltration. In other words, this process resembled inflammation of the liver much more than cirrhosis of the liver; the latter I look upon as a degenerative rather than an inflammatory lesion with response chiefly on the part of connective tissue. Finally, in a third section taken at a distance from the others (Fig. 3),

the liver appears entirely normal. The portal space contains the hepatic artery, portal veins, bile ducts and the surrounding hepatic cords arranged in a perfectly normal pattern. The Kupffer cells are a little more prominent throughout the entire liver than they should be, but they do not contain any pigment. There is no hemosiderosis.

Figure 4 is from the spleen and shows a central arteriole. There should be a surrounding follicle but none is present; instead there is "lymphocytic exhaustion" and the follicle is replaced by lymphocytes, many large mononuclear cells, and occasional heterotropic megakaryocytes—typical megakaryocytes were noted throughout the spleen. There are also nucleated red blood cells which indicate that the spleen was the site of extramedullary hematopoiesis.

In a section of bone marrow (Fig. 5), marked hyperplasia of megakaryocytes is seen. Large mononuclear cells such as were seen in the liver are present; these may be immature or degenerating megakaryocytes. The myeloid and erythroid elements in the bone marrow show a lack of maturation. There are very few well developed cells of either the red or the white series. Figure 6

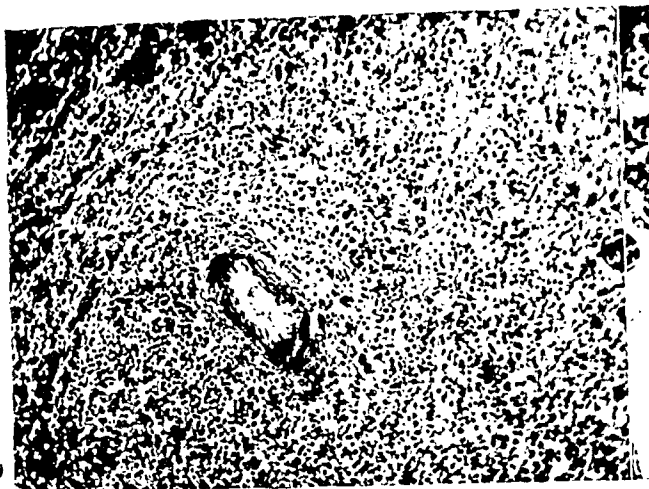


FIG. 4. Low power view of a section of the spleen. Note the absence of the normal structure about the arteriole. x 47.

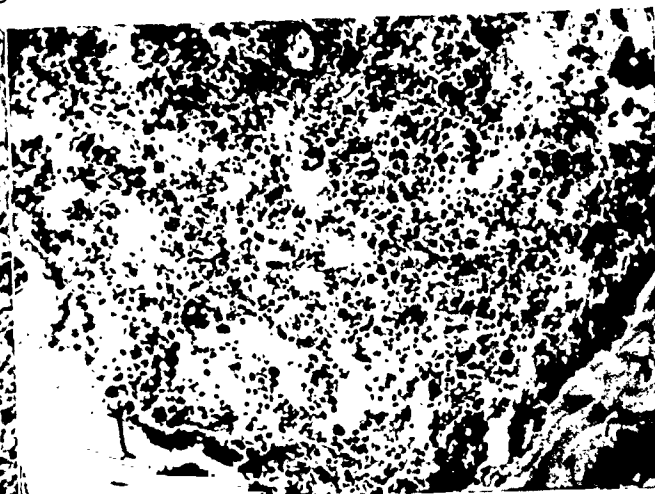


FIG. 5. Low power view of a section of bone marrow showing marked hyperplasia of the megakaryocytes. x 47.

is a higher power view to show these cells with a ragged outline and multiple, sometimes hyperchromatic nuclei. They are thought to be megakaryocytes. Degenerated, necrotic forms of these same cells are also seen. Occasionally, there are thrombi in the small capillaries of the bone marrow, liver and spleen. That the thrombi were present for a rather long time is evidenced by the foci of calcification in the bone marrow. These areas were apparently necrotic at first and subsequently became calcified.

To interpret the nature of the pathologic lesions in this case is extremely difficult. First, there was irregular destruction of the liver with almost complete loss of structure in some foci and none in others; there was also moderately active regeneration. Second, although limited focal deposits of hematin were noted in a few Kupffer cells, this finding may have been an artifact since there was no general hemosiderosis of the liver or the spleen. Third, there were exhaustion of the lymphoid tissue of the spleen and fibrosis of the splenic pulp. Although large mononuclear cells and multinucleated cells were present in the liver and the spleen, there was no evidence of a granulomatous process in any of the tissues. Extremely active erythrophagocytosis was seen in the

spleen, many of the large mononuclear cells having been filled with partially digested red blood cells. Fourth, hyperplasia of the megakaryocytes in the bone marrow was prominent. There was suppression of maturation of cells of the red and white cells series; focal calcification, capillary thrombi, and cellular necrosis were

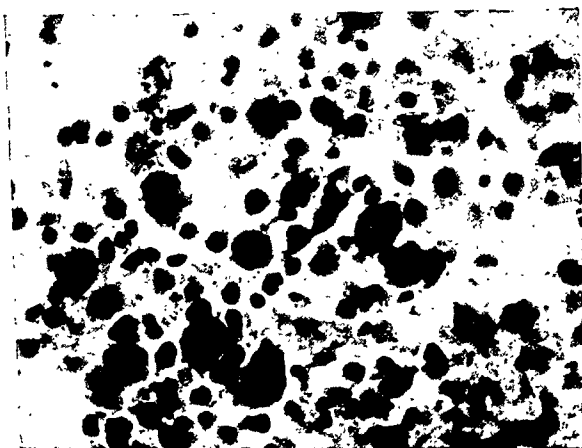


FIG. 6. High power view of the section seen in Figure 5. Note the large megakaryocytes, some of which are multinucleated. x 97.

found in the bone marrow. No living agent was demonstrated in these tissues.

In other words, this man had a disease causing enlargement of the liver of at least six years' duration, associated with purpura and arthritis for three years, eventually leading to portal hypertension and esophageal varices, and terminating in hepatic failure. During the same period of time he appar-

ently had malaria, an illness diagnosed as infectious mononucleosis, and after his first operation he had some form of pulmonary disease. The problem as I see it is to decide whether one diagnosis can account for all the major changes recorded in this patient's history since 1939; in other words, to answer the question that was asked in the clinical discussion: Was there a relation between the disease of the liver and the rest of the patient's illness, or did he have two or more diseases in sequence or together?

Malaria cannot be established in this case for the sections do not show any of the pathologic changes which are characteristic of chronic malaria. Infectious mononucleosis, if ever present, left no residuum. The disease which involved the joints was not destructive; when the knee joints were opened the articular cartilages were well preserved, and when the synovial tissue was examined microscopically, no evidence of inflammation was found. I would, therefore, feel reasonably safe in excluding rheumatoid arthritis. Likewise, no lesions suggestive of syphilis were present. If the patient had infectious mononucleosis and malaria, I think it must be assumed that they were intercurrent, unrelated diseases, although it is worthy of note that one case of supposed association of malaria and Henoch-Schönlein purpura has been reported in the Bulletin of the Veteran's Administration. It was the only case I could find. The pulmonary disease was probably an event of the patient's postoperative course—atelectasis, pulmonary embolus or bronchopneumonia. If the foregoing hypothesis is accepted, the purpura and the hepatic disease remain unexplained.

As far as I could determine going through the Quarterly Cumulative Index for the last fifteen years, there were only two titles which suggest that an autopsy had ever been performed on a patient with Henoch-Schönlein purpura, and both of the articles

were in journals which were not available. I was, therefore, unable to find an adequate description of the pathologic anatomy of the disease. In going through all of the textbooks and monographs on the subject, the only information which could be obtained indicated that patients with Henoch-Schönlein purpura may have pericarditis, edema of the glottis and cerebral hemorrhage. It is stated that 20 per cent of them die of glomerulonephritis, but again I could not find any pathologic description or photomicrographs of kidneys from patients who had died with glomerulonephritis in association with this type of purpura.

I agree with the clinical diagnosis that this patient had Henoch-Schönlein purpura. If a significant number of patients develop an inflammatory disease of the kidney in association with Henoch-Schönlein purpura, why should not an occasional patient develop an inflammatory disease of the liver? In this case there was an inflammatory disease of the liver. It represented an example of so-called toxic or multilobular cirrhosis, or of a hepatitis, rather than an example of Laennec's cirrhosis. I believe, therefore, that in this patient the purpura on the one hand and the progressive, destructive hepatitis on the other were directly associated, and part of a single disease process.

DR. ALEXANDER: As you know, Sir William Osler was most interested in this disease and one might predict that a man of his scientific curiosity, confronted with a disease characterized variously by purpura, urticaria, erythema multiforme, abdominal pain, joint pains and nephritis would repeatedly refer to it throughout some twenty years of his medical career. He followed his cases carefully and in 1914 assembled all that was known about the disease at that time; and although he quoted a description of the pathologic findings in the kidneys of five patients who had Henoch-

Schönlein purpura, nowhere was there a complete autopsy report. I repeat, therefore, that this case takes on special significance indeed, for it clinically represented without doubt Henoch-Schönlein purpura and its associated lesions.

DR. WOOD: Dr. Moore, would you comment on the relationship between the thromboses in the liver in this case and those which Rich has described in sulfonamide nephroses.

DR. R. A. MOORE: The thromboses in this case were platelet and fibrin thrombi in capillaries not surrounded by any inflammatory reaction. I do not believe that they are related to the type observed by Rich. I would not put this patient's disease in the same category with lupus erythematosus or periarteritis nodosa.

DR. C. V. MOORE: Were you at all disturbed in your interpretation by the fact that in none of the diseases like lupus erythematosus or periarteritis nodosa, even though there may be considerable involvement of the liver, there is no associated cirrhosis?

DR. R. A. MOORE: No, since I do not look upon the changes in this case as those of ordinary cirrhosis; I consider the process here as a hepatitis and attribute the fibrosis

to the fact that the disease went on for a number of years.

DR. C. V. MOORE: In lupus erythematosus or in periarteritis nodosa is fibrosis like this seen?

DR. R. A. MOORE: I have neither observed it nor have I seen it described. Glomerulonephritis is likewise uncommon; the lesion in the kidney in those diseases is distinct from that of glomerulonephritis.

Final Anatomical Diagnosis: Anatomic findings consistent with diagnosis of Henoch-Schönlein purpura; multilobular cirrhosis of liver; serosanguineous ascites (2000 cc.); generalized icterus, advanced; ruptured esophageal varices; altered blood in the stomach and intestines (2000 cc.); lymphoid exhaustion and fibrosis of spleen; erythrophagocytosis in spleen; hyperplasia of megakaryocytes in bone marrow; heterotopic megakaryocytes in liver and spleen; depression of maturation of myeloid and erythroid cells in bone marrow; recent hemorrhage in the superior and posterior mediastinum, abdominal wall, retroperitoneal space; hyperplasia of the tracheobronchial, periaortic, peripancreatic, periportal, and mesenteric lymph nodes; fibrous obliteration of the pericardium, partial.

Case Reports

Agranulocytosis Occurring after Exposure to a D.D.T. Pyrethrum Aerosol Bomb*

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WITH the current release of surplus material by the War Department, the civilian markets have been flooded with various insecticidal preparations containing D.D.T. (dichlorodiphenyl trichloroethane). Since its introduction in Europe in 1939 and in America in 1942, the investigations relative to the toxic effect of D.D.T. on laboratory animals and man have been extensive. The consensus is that it is relatively safe,^{4,20,21,33,22,37,32,23,24,29,26} however, recent reports indicate that it is not as innocuous as formerly thought.

The purpose of this report is to present a case of agranulocytosis which developed in a twenty-two year old, white male after exposure to the spray of a D.D.T. pyrethrum aerosol bomb. Evidence is presented which incriminates this preparation as the offending agent.

CASE REPORT

A white, twenty-two year old man, a University student, came into the emergency room of University Hospital with the complaints of sore throat and tongue of twenty-four hours' duration with associated fever and chilliness.

Ten days before the onset of the presenting symptoms the patient had sprayed his apartment with an aerosol insecticide bomb which contained D.D.T., pyrethrum extract and difluorodichloro methane (Freon). During the interim between exposure to this insecticidal material and the onset of the symptoms the patient went about his usual school activities without appreci-

able difficulty. The day preceding his seeking medical attention he noted a small ulceration on the tip of the tongue. That evening he developed sensations of chilliness which persisted the next morning. The ulceration on the tongue progressed with generalized soreness of tongue and throat, which was accentuated when he attempted to eat. His temperature rose to 101°F. That afternoon, the second day of symptoms, he came into University Hospital.

On admission the temperature was 102.6°F. There was an ulceration 4 mm. in diameter with greyish membrane on the tip of the tongue. The oral pharynx was moderately hyperemic. The submandibular and angular lymph nodes were palpable and slightly tender.

The initial white blood count was 3,850 with the following differential: Neutrophils 1 per cent, eosinophils 2 per cent, lymphocytes 75 per cent, monocytes 22 per cent. (Fig. 1.) Throat cultures were positive for *Staphylococcus aureus* and non-hemolytic streptococcus.

Penicillin, 30,000 units i.m. every three hours, was instituted. Local therapy to the oral lesions consisted of painting with 1/4 per cent Gentian violet and warm Seiller's throat irrigations.

By the third hospital day the total white blood count had risen to 6,150, with 24 per cent neutrophils, 1 per cent basophils, 5 per cent eosinophils, 1 per cent myelocyte "C," 27 per cent small lymphocytes, 42 per cent monocytes, by the supravital technique. The red blood count was 4,910,000 with 14.6 Gm. of hemoglobin. The platelets were 898,160 per cu. mm. There was parallel improvement clinically with decline of the temperature to normal and healing of the oral lesions. The granulocytes gradu-

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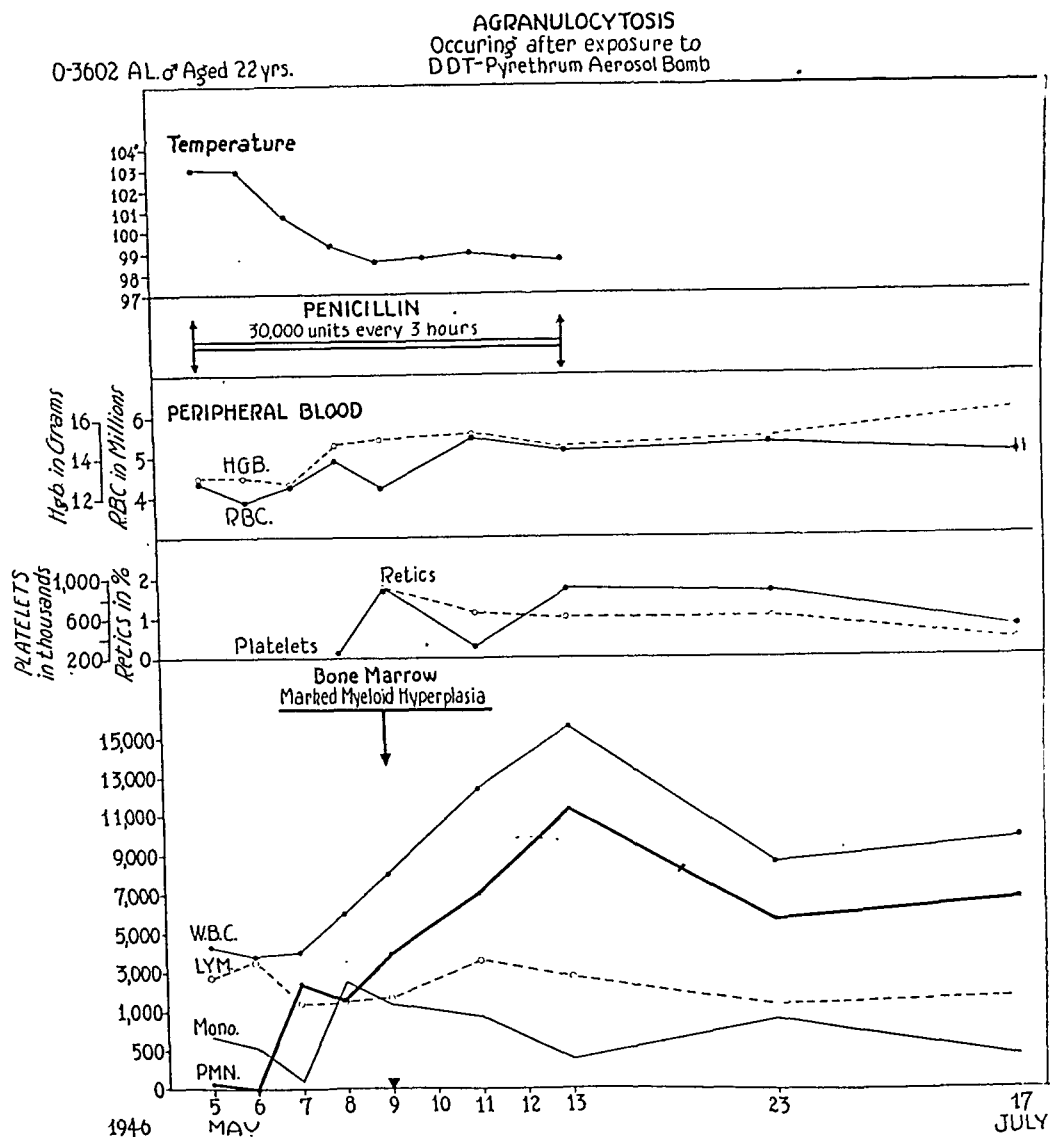


FIG. 1. The first hematologic studies were made eleven days after exposure to the aerosol bomb spray.

ally increased with a corresponding fall in the compensatory absolute monocytosis.

Examination of the sternal bone marrow, using the supravital technic, on the fifth hospital day showed a marked increase in the myeloid cell series, which were mainly at the "C" level. This hyperplasia was reflected in the overcompensatory peripheral blood findings four days later, at which time the white blood count was 15,600 with 73 per cent neutrophils.

Ten weeks after discharge the patient continued to remain clinically well and the hematologic studies at that time were as follows: total white blood count 9,600; with the following supravital differential; polymorphonuclear neutrophils 71 per cent, eosinophils 6 per cent, small lymphocytes 17 per cent, intermediate lymphocytes 1 per cent, monocytes 5 per cent. The red

blood count was 5,090,000 with 16.3 Gm. of hemoglobin. The platelets were 498,820 per cubic mm.

COMMENT

Agranulocytosis. The diagnosis of "ideopathic agranulocytosis" was very commonly made during the decade between the description of the syndrome by Schultz in 1922²⁷ and Kracke's^{15,16} and Madison's and Squier's observations¹⁷ that certain benzene ring compounds played a significant etiologic rôle. Now that many organic chemicals and metallic drugs have been demonstrated as potentially capable of causing profound depression of myelopoiesis in certain hypersusceptible individuals, a history of such

exposure must always be sought. In this case it was only after persistent questioning over several days that the history of exposure to the aerosol bomb was obtained. The patient then remembered using it with a cut on his hand and with some direct skin contamination. No medication had been taken during the preceding four weeks. There had been no exposure to any industrial chemicals, and no evidence of any bacterial or virus infection preceding the onset of the oral lesions.

In previous clinical studies of agranulocytosis in this laboratory, it was shown, through a correlation of bone marrow and peripheral blood observations, that approximately two weeks may be required for the maturation of the immature myeloblast to the mature, five-lobed, polymorphonuclear neutrophilic leukocyte.⁹ In this instance the exposure to the spray of the aerosol bomb occurred ten days preceding the onset of clinical symptoms. The insult to myelopoiesis undoubtedly occurred then, but was not reflected symptomatically until the delayed peripheral neutropenia developed. By the time the peripheral neutropenia was manifested through the onset of the oral lesions, chilling and fever, a compensatory monocytosis plus regeneration of the myeloid elements was already occurring; followed, after a brief latent period, by beginning regression of the clinical syndrome. The bone marrow fifteen days after the original exposure and five days after appearance of symptoms revealed the myeloid elements in a stage of rebound hyperplasia, even though there was still a moderate peripheral neutropenia (24 per cent). This bone marrow recovery with hyperplasia was only fully reflected in the peripheral blood several days later. (Fig. 1.)

The D.D.T.-pyrethrum mixture is much more effective as an insecticide than either chemical used alone. The pyrethrum acts as a contact insecticide, thus allowing the

slower acting D.D.T. to exert its effect as a central nervous system toxin. The aerosol insecticide bomb to which this patient was exposed was of the type that was manufactured for the armed forces under specifications of the War Department. The small metal cylinder, 6 cm. long, contained 10 Gm. net contents. On the carton was stated, "Aerosol Insecticide Bomb containing D.D.T. and Pyrethrum extract . . . Ingredients active 16½%, inactive (difluorodichloro methane) 83½% . . . Caution: avoid contact with skin and don't spray on food. Avoid excessive breathing of spray. If taken internally, use emetic of mustard." The metal pin in the open end of the cylinder is broken off to release a spray cloud of about six seconds' duration. Warning is made to hold spray away from the operator. Inquiry from the manufacturers revealed that in addition to the above ingredients the bomb contained sesame oil and lubricating oil (SAE 30).*

Thus, any of the ingredients—the D.D.T., the pyrethrum, the sesame oil, the Freon, or the lubricating oil, (SAE 30)—could be indicated as the noxious agent. Neal²⁵ states, "There is no definite evidence which should indicate that D.D.T. produces any marked or characteristic change on the blood cell picture. Studies of the blood constituents during chronic subacute D.D.T. poisoning in dogs reveal only a drop in hemoglobin, which over a period of days results in hypochromic anemia. It is considered that this anemia is related indirectly to the dietary deficiencies produced by prolonged anorexia and inadequate food intake during repeated periods of tremors and convulsions." Similar observations have been made by Telford.³¹ Acute D.D.T. toxicity has been characterized predominantly by central nervous system irritability—nervousness, tremors and generalized convulsions. In chronic toxicity in animals two path-

* Manufactured by Kidde Manufacturing Co., Inc.

ological lesions, centrolobular necrosis of the liver, and, less frequently, focal necrosis of striated muscles, have been most commonly observed.²

Three deaths have been cited in England. In two instances D.D.T. preparations were taken with the intent of suicide. In one, 6 ounces of 20 per cent D.D.T. in cyclohexanone was taken and in the other an unknown amount of 6 per cent D.D.T. in kerosene. In both death was attributed to the solvent.² In the third case 1 ounce of 5 per cent D.D.T. in kerosene was ingested by a one and one-half year old child resulting in death within four hours.¹¹

Case⁵ and Hill and Robinson¹¹ have shown in their studies in both man and animals that either direct skin contact or ingestion of mixtures of D.D.T. in oil can produce significant toxic effects. In a carefully controlled series of observations carried out on two normal human subjects in an experimental chamber, Case noted among other changes a granulocytopenia (6,900 to 1,412 and 6,528 to 1,512), which developed in both men on the third to fourth days following a forty-eight-hour exposure to a D.D.T.-oil mixture. There was a delayed absolute lymphocytosis up to 5,170 and 5,208 per cubic mm. on the nineteenth and forty-ninth days, respectively. From the clinical and experimental data presented by these investigators it appears that the toxicity of D.D.T. may be enhanced by mixing with certain oil solvents, and that among other organs the bone marrow may be affected. Case presents the first and only positive evidence to date suggesting the value of careful hematologic studies in the early recognition of D.D.T. intoxication.

Pyrethrum, a powdered insecticide obtained from the flower-heads of members of the chrysanthemum family, has been noted by Chevalier⁶ to be toxic to warm-blooded animals only when administered intravenously in large doses. It has also caused mental

confusion in those exposed to long periods of heavy concentrations. No evidence has been reported suggesting any noxious effects on the blood elements.

Difluorodichloro methane (Freon) is commonly used as a refrigerant. Kehoe¹³ states that levels as high as 20 per cent in air have caused no apparent deleterious effect in animals. Humans have experienced exposure to concentrations of 8 to 12 per cent without appreciable harm. There have been recently noted three instances in which serious burns to the hands resulted from improper use of the aerosol bomb.^{14,19} In all instances, the hand was placed over the suddenly released pyrethrum—D.D.T.—Freon spray cloud. The Freon caused immediate freezing of the fingers or hands which resulted in third degree burns. In one case the two distal phalanges of an index finger were sacrificed.

Sesame oil is a frequently used solvent for pharmaceutical purposes, particularly in hormone therapy and no deleterious effects have been ascribed thus far to it.³⁶

Therapy. A number of recent reports have cited the efficacy of the newer forms of antibiotic therapy in tiding over the acute phase of a toxic agranulocytosis until the bone marrow can recover spontaneously.^{1,12,30,18,7,28,10,34,3,35} This case is another to be added to the list of therapeutic successes. However, it should be emphasized that this *antibiotic reprieve* is effective only if the insult is of a mild and temporary nature. If the damage to the bone marrow is so potent and massive that myelopoiesis is more than transiently impeded or destroyed, this temporary suppression of secondary bacterial invaders does not guarantee permanent recovery.

Two such instances of failure have been seen recently in this clinic. The first was a thirty-four year old white woman (G.K.-0.7642) who had taken five to six "B. C. Headache Powders" (acetanilid) daily for

the past year. When she was first seen she had only 700 circulating white blood cells, with no granulocytes in the differential count. Examination of a specimen of sternal bone marrow with the supravital technic revealed only 0.5 per cent myeloid elements. There was a generalized pan-marrow hypoplasia. Blood cultures were positive on four occasions for *Klebsiella pneumoniae*, in spite of intensive sulfadiazine (6 Gm. daily) and penicillin (400,000 units daily) therapy. Streptomycin therapy (totaling 9,500,000 units) was begun five days before death. Blood cultures became negative on the third day and remained sterile the last two days of life, although the bone marrow and peripheral blood pictures failed to respond. Autopsy findings were consistent with the clinical diagnosis and observations.

In the second instance a forty-one year old white woman (E.U.-0.7325) developed severe angina with agranulocytosis (white blood count 200) after a two-weeks' course of thiouracil (0.2 Gm. daily) for hyperthyroidism. Six months previously she had taken 16.8 Gm. of thiouracil over a six weeks' period for the same symptoms, at the conclusion of which she had an episode of "acute tonsillitis and fever" of questionable etiology and without blood cell data having been obtained. From the subsequent course of events it may be assumed that the myeloid elements of the bone marrow had been sensitized by the first course of thiouracil, and when the second course was instituted, of considerably smaller dosage, the injury to these elements was disproportionately great and severe. The red blood cells and platelets remained within normal limits. The overwhelming infection after twenty-four hours of intensive penicillin therapy showed no progression and slight clinical improvement. The patient expired suddenly, however, at the end of this brief hospitalization, after two generalized convulsions. At postmortem the brain showed

bleeding into Virchow-Robin's spaces with focal bleeding in the brain substance and subarachnoid space. There was marked universal toxic hypoplasia of all bone marrow.

CONCLUSIONS

1. A case of agranulocytosis occurring after exposure to an aerosol insecticide bomb is presented. The bomb contained D.D.T., pyrethrum, sesame oil, petroleum oil (SAE 30) and difluorodichloro methane (Freon). The known toxic effects of these ingredients are discussed briefly. The time interval of the onset of symptoms after exposure, the inability to discover contact with any other known myelotoxin, the lack of any signs of an acute infection before the onset of oral lesions, along with the recent experimental evidence that D.D.T. in oil may cause a granulocytopenia in man,⁵ are factors incriminating this preparation as the toxic agent.

2. At least three instances of severe burns to the hands and fingers resulting from the misuse of aerosol bombs have been observed. These were due to the difluorodichloro methane (Freon).

3. The value of antibiotic therapy as a temporary emergency inhibitor of secondary bacterial invaders during the period of transient agranulocytosis is emphasized and illustrated in the case presented. In addition to the limitations of specific bacteriologic susceptibility, antibiotics are effective at best only when the toxic depression is very transitory and the bone marrow's recuperative powers are permitted to assert themselves promptly after the insult. Two instances of fatal agranulocytosis, one due to prolonged administration of acetanilid and another to sensitivity developing during thiouracil therapy are noted as examples of failure with antibiotic and all other adjunct therapy.

4. Evidence is beginning to accumulate

which indicates that D.D.T.-oil mixtures are potential toxins to bone marrow as well as to other organs. With the widespread and indiscriminate use of these preparations at the present time, the granulocytopenic syndrome probably will be observed more frequently. Careful hematologic studies in those working in heavy or repeated exposure are indicated to detect early toxic effects and to prevent irreversible bone marrow damage.

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Lupus Erythematosus Disseminatus in a Male*

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A CASE of disseminated lupus is reported as to its symptoms, clinical course and the pathological changes as seen at postmortem.

CASE REPORT

A white male, age twenty, entered military service in January, 1943. His habits were excellent. Father and mother were living and well. He was the only child. The only allergy history was that the maternal grandfather had asthma. He had had mumps, measles and chickenpox in childhood without complications. Tonsillectomy and adenoidectomy were performed in 1932.

In November, 1943, nine months after entering the service, he noted that he had pains in his ankles and knees after hikes which would persist for a couple of days. The following month, December, he noticed some tiny, red, elevated lesions on both forearms. These gradually increased in size and after about two months receded.

He first reported on Sick Call on February 5, 1944, while in England, with chills, high fever, vomiting, and tender painful joints, generalized ecchymotic rash over the extremities, petechiae on trunk, and generalized lymphadenopathy. Meningococcemia was suspected but his spinal fluid and blood culture were negative. He was treated with sulfonamides. The rash faded and disappeared within a week. Fever of between 100° and 101°F. persisted. Two weeks later he developed fever (104°F.), chills, and an erythematous type of rash appeared, distributed over the entire body. The diagnosis of "erythema multiforme" was made. This acute phase was followed by a two-week period during which he ran a low-grade fever, rapid pulse, low white

count (below 4,500), and slightly elevated sedimentation rate. Five weeks after the acute onset he suddenly developed sharp pain in the anterior chest with a pericardial friction rub associated with a soft, blowing, systolic murmur at the apex. After six days a pleural friction rub was detected over the left lower chest. Electrocardiograms did not support a diagnosis of pericardial effusion. X-rays of the chest showed an increased density over left lower chest. These symptoms subsided and during the last two weeks in March and all of April the patient felt well except for occasional joint pains and slight elevation of temperature.

He was evacuated to the United States and admitted to Billings General Hospital on May 16, 1944, with a transfer diagnosis of: "Acute rheumatic fever with erythema multiforme, acute pericarditis, and left pleural effusion." On the boat he had gone on deck to get some sun and had noticed that the previous quiescent lesions on his forearms had become bright red.

Physical examination revealed the following: Weight 140 pounds, height 72 inches, temperature 98.6°F., respirations 22, and blood pressure 115/72. There was a brownish discoloration over the bridge of the nose and also over the upper chest (this was more prominent when examined in a not too bright light). On each forearm were small scaly patches sharply defined with bright redlined borders. On the left buccal surface there was a sharply defined flat, shallow ulcer with white streaked center and red border which was painful. The submaxillary and cervical glands were enlarged but not tender. There was a limitation of excursion of the left lower chest but no physical signs of fluid. The heart was normal in size, shape, position and sounds. The abdomen was negative and lower

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extremities revealed no changes. The shoulders, elbows and hands were painful but presented no swelling or redness. Urine was normal chemically and also the sediment; red blood count 4,600,000; white blood count 5,000 with normal differential. Sedimentation rate was 20 mm. in one hour; total protein 7.2 A.G. ratio normal. Chest x-ray was reported as showing normal lung parenchyma, some calcified nodes in right hilum, and heart shadow normal.

During his first two weeks at this hospital he ran very slight elevation of temperature, ate well, gained weight and generally felt he was improving. On August 8th, he developed transient edema of both eyelids followed by painful herpetiform lesions on his buccal surfaces. One week later he complained of pain in his left arm and two somewhat hard nodules appeared on the extensor surface of the left arm. On palpation these were slightly elevated, indurated, and tender. They were reddish in color and persisted for three days. A muscle biopsy done at this time was reported as showing diffuse angiitis of periarteritis nodosum type. Early in August, signs of pleural exudation appeared in the left chest; i.e., limited expansion, absence of breath sounds, percussion impairment and diminished fremitus. Thoracentesis confirmed these clinical findings and from August 8th to November 30, 1944, nine chest taps were done with an average of 1,500 cc. for each aspiration.

There was nothing unusual in the pleural fluid and animal inoculation was negative. During the period of August through November, the heart rate was more rapid. A systolic murmur was heard over the apex and into the axilla; a gallop rhythm appeared. There was a period when the heart sounds became inaudible and cardiac dullness seemed much increased and a pericardial effusion was suspected. The heart sounds reappeared without aspiration. During December, 1944, the joints again became very tender; cervical and epitrochlear lymph nodes became palpable. A node was removed for biopsy which was reported as reactive lymph node with marked hyperplasia. "While the lymph node is purely one of non-specific reactive nature and each of the microscopic cellular vascular and collagen changes alone

might have little significance, the sum of all the minutiae even though necrosis is not present would be consistent with a diagnosis of Dermatomyositis or Lupus Erythematosus Disseminatus" (William Antopol, Major, AUS, Chief of Laboratory Service).

A purulent discharge appeared from the left ear, was diagnosed otitis media, which promptly responded to penicillin therapy. A gradual reduction in red cells and hemoglobin was observed. During the following month he showed general improvement and this remission lasted about thirty days.

The next relapse was ushered in by a recurrence of the herpetiform painful ulcers in his mouth and throat. Purulent sputum appeared, fever was higher, pulse fast, the patient had headache, felt weak, and for the first time edema of his extremities and fluid in the abdomen were present. The urine, for the first time, in February 1945 showed evidences of renal involvement by the presence of albumin, red cells, and casts. The red blood count was 3,200,000; hemoglobin 71 per cent; white blood count 4,500; sedimentation rate 30 mm. for one hour; total proteins 7.3 per cent; albumin 3 per cent; globulin 4.3 per cent; non-protein nitrogen 36 mg. per cent; urea 14 mg. per cent; cholesterol 100 mg. per cent.

During March his sedimentation rate rose to 60 mm. per hour; red blood count was 2,700,000; hemoglobin 56 per cent; total proteins 5.6 per cent with albumin 1.6 per cent; and globulin 4 per cent. Transfusions of whole blood and also plasma failed to divert the downward course and the patient died March 23, 1945, seventeen months after onset.

COMMENTS ON CLINICAL COURSE

Fever. At the onset the temperature remained elevated for twenty-seven days except for four mornings when the reading was either normal or subnormal. This period was followed by two months of normal temperature range except for two consecutive days of elevation. This was followed by ten weeks of continuous fever. During the following month the temperature was again normal. During the rest of

his illness he ran fever with the exception of five periods of approximately ten days each. There were seven remissions of variable length, judging by the temperature curve.

Curiously enough, during the period of early pericardial and pleural involvement, he had only five days of fever followed by two months of normal temperature. Early in August and through November, 1944, he was having pleural exudation with frequent aspirations and three of the ten-day fever free periods occurred during these months. (Fig. 1.)

Skin Manifestations. In December, 1943, small, red, elevated lesions appeared on both forearms. On February 6, 1944, at time of onset, a petechial rash appeared over trunk with ecchymosis over lower extremities. On February 21st, after two weeks of sulfadiazine medication, a diffuse erythematous rash appeared with painless buccal ulcers. At the time this was considered a drug rash. On March 4, 1944, a dry scaly flush appeared over the face and was attributed to tear gas to which the patient had been exposed. On May 16th, a definite butterfly lesion over the nose and malar surfaces was observed. There were sore, painful, buccal lesions present. On each forearm were scaly patches with bright red borders. On August 18th, painful herpetiform buccal ulcers reappeared. Two painful nodules appeared on left forearm. On February 3, 1945, painful herpetiform buccal ulcers recurred.

Joints and Muscles. No marked joint swelling or redness appeared but during most of the course of the disease joint and muscle tenderness was a prominent symptom.

Laboratory Studies. The blood showed a persistent tendency toward leukopenia with occasional rises, associated with secondary changes such as sore throat, colds, or bronchial purulent material. The red cells

showed a very slowly developing anemia with anisocytosis, poikilocytosis and hypochromia. The sedimentation rate in one hour varied from 15 mm. to 30 mm. throughout, except terminally when it rose to 62 and 70 mm. per hour. Blood cultures were all negative.

X-ray Studies. The earliest study is dated February 27, 1944, and showed normal lung with a small oval calcified deposit at right base. On March 13, 1944, evidence of a pneumonic process in the left lower lobe with pleurisy and effusion is recorded. A definite change is noted in the appearance of the heart in the upright and prone positions, apparently due to a small amount of pericardial fluid causing a widening about the base of the heart. Film of the chest on May 20, 1944, shows small calcified parenchymal scar in lower right lung with small calcified nodes at the right hilum. Impression of film taken June 16, 1944, was normal chest. On August 11, 1944, x-ray showed massive left pleural effusion with mediastinal displacement to right. X-ray report of October 23, 1944, revealed fluid extended from apex to base without mediastinal displacement; the December 4, 1944, report stated multiple fluid levels are identified; the February 26, 1945, report revealed pleural thickening in the left hemithorax. There was very slight increase in the transverse diameter of the cardiac shadow.

Serial Electrocardiographic Changes. First electrocardiogram taken February 29, 1944, approximately three weeks after admission overseas, revealed slightly low and rounded T-waves. Another electrocardiogram four days later revealed further slight decrease in the voltage of the T-waves. It was during this time that a pericardial friction rub and a soft blowing systolic murmur were noted. An electrocardiogram taken May 19, 1944, shortly after admission to Billings General Hospital, showed a return of T-waves to normal amplitude. At this time, examina-

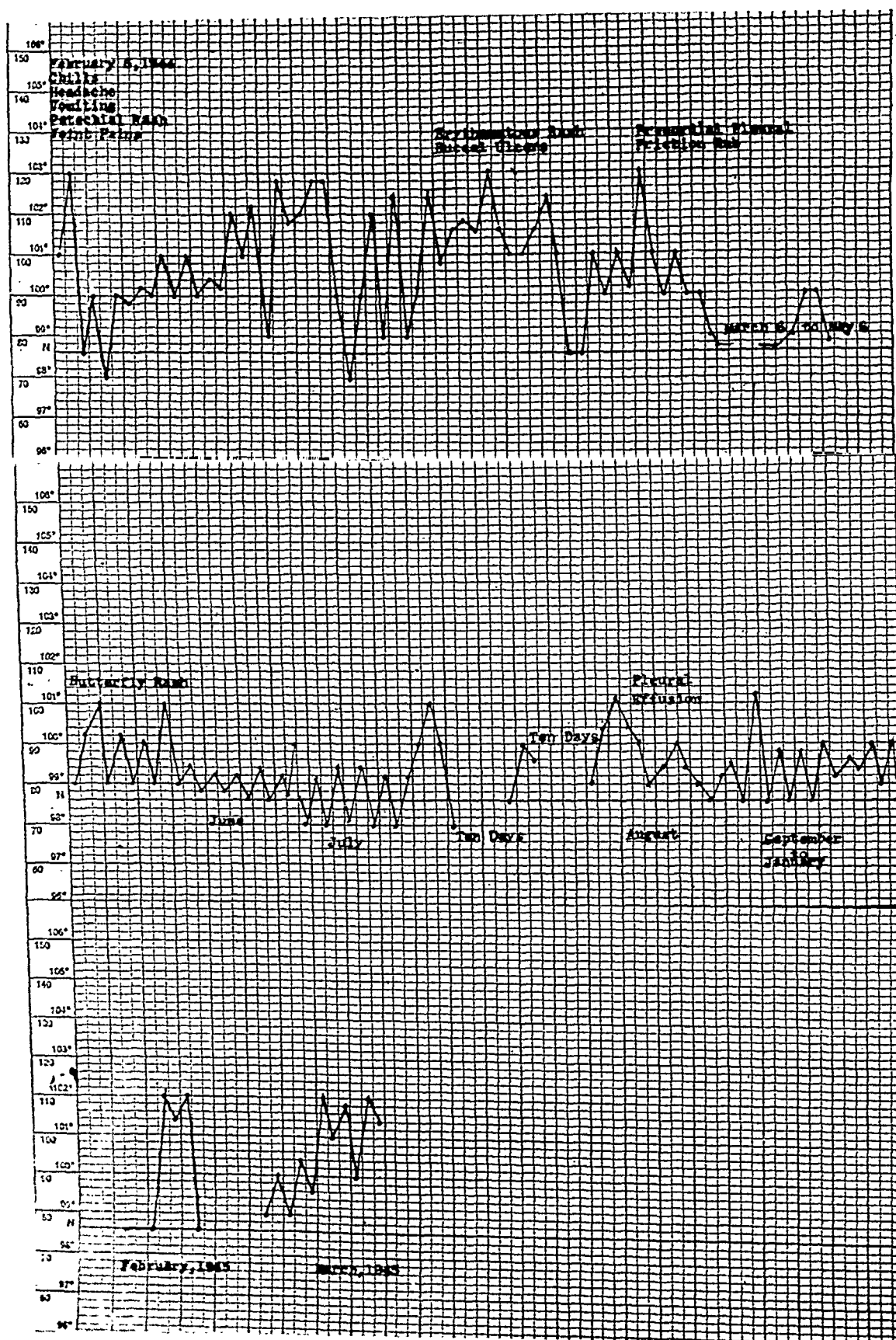


FIG. 1. Showing clinical course of patient with lupus erythematosus disseminatus.

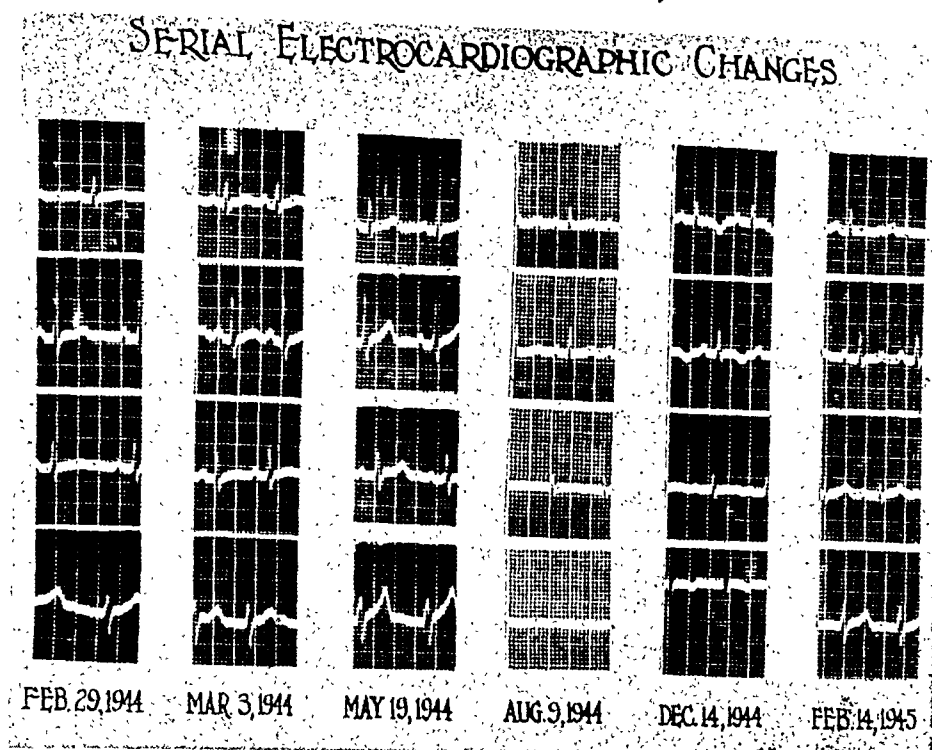


FIG. 2

tion of the heart and lungs was negative. During August, 1944, the patient developed a massive left pleural effusion with a shift of the mediastinum to the right. All the QRS complexes and the T-waves in leads I and II were diminished in amplitude and in leads III and CF-IV were almost isoelectric. The heart sounds were very distant due to the massive left pleural effusion and the right border of the heart showed pulsations of good amplitude on fluoroscopic examination. At this time it was believed that the diminished QRS complexes and low T-waves were at least partly due to the massive pleural effusion. On December 4, 1944, further changes were noted and T-I and T-II had become deeply inverted, T-III was diphasic and T in CF-IV was deeply inverted. An electrocardiogram on February 14, 1945, revealed T-I still inverted with T in leads II, III and CF-IV upright. The last three serial tracings are compatible with a pericardial effusion and the subsequent development of a thickened pericardium. (Fig. 2.)

Treatment. During the first three weeks of his illness the patient received sulfadiazine

in standard doses. Sodium salicylate was substituted for the sulfa and continued until his arrival to the United States. Here his orders read, "Complete bed management; high caloric, high protein diet; sodium salicylate Gm. iv in divided doses; multi-vitamin capsule t.i.d.; and 3 cc. liver extract tri-weekly." In August, it was decided to give him a course of penicillin consisting of 1,500,000 units, which had no effect on the course of his disease. He felt more comfortable when on salicylates. The mouth lesions were very resistant to treatment and ran their course unaffected by any therapy tried, such as topical sulfa, penicillin, and all the usual mouth washes. Plasma and washed cells were given in the latter part of the course.

AUTOPSY REPORT

General. The skin over the face was roughened and there was a muddy appearance starting from the area of the nose and extending over almost the entire sides of the face. There was a similar appearance over the sternum but here there were dis-

persed whitish areas. Upon incision the subcutaneous fat was yellow and scant. The muscles were red and well developed. There was a considerable accumulation of yellowish viscid fluid in the abdominal cavity. All organs were in their normal relationship. There were adhesions between the anterior surface of both lobes of the liver and the diaphragm and anterior abdominal wall. The spleen was also adherent to the diaphragm and could be separated with moderate ease. The diaphragm was at the level of the sixth rib on the left and at the fifth on the right. The mesenteric lymph nodes were prominent. The intestines and intra-abdominal fat were edematous; this was more marked in the colon. The diaphragm was also thick and edematous. There were universal adhesions between the visceral and parietal pleura on the left side which completely obliterated the pleural cavity except on the posterior portion where there was considerable fluid. There was a moderate amount of fluid in the right pleural cavity. The mediastinum was in the midline. The pericardium was thick and edematous. There were universal adhesions between the pericardium and the epicardium with a few pockets of inspissated fluid in the cavity. A culture was taken from one of these pockets. The parietal pericardium on the right reached 1 cm. in thickness and could be taken off in the form of a white opaque plaque.

Lungs. In the upper portion of the right middle lobe was a small pleural calcific nodule. In the interlobar fissure there was an accumulation of greenish-brown inspissated material. This communicated with a cavity, 15 mm. in diameter, which was filled with similar material and was delimited from the adjacent tissue by a membrane 1 mm. in thickness. The cavity appeared to be in the substance of the upper lobe. The trachea and bronchi were congested. The tracheal-bronchial nodes were

enlarged and the one on the left was calcified.

Heart. As mentioned previously, the pericardium was markedly thickened and edematous. The heart, with the pericardium and ascending aorta, weighed 780 Gm. The epicardium was also edematous. On the posterior wall of the right ventricle was an irregular area of thickened gray endocardium. In the angle made by the origin of the chorda tendineae of the posterior leaflet of the valve and the ventricle wall, there was a flattened rough granular vegetation, some of which extended on to the chord. There was slight fusion between the anterior and left cusps of the pulmonary valve. There was considerable hypertrophy of the left ventricular wall. There were large scattered areas of thickened and gray endocardium throughout the ventricle but more marked about the base of the papillary muscles and behind the leaflets of the mitral valve. At the base of the papillary muscle of the anterior leaflet of the mitral valve was a flat vegetation 1 cm. in diameter. Scattered over the endocardium at the apex were numerous small areas of roughening with some small vegetations. Some of the chordae tendinae of the mitral valve were short and thick and an occasional one had a fusiform thickening. On the anterior surface of the anterior leaflet of the mitral valve was another flat vegetation. In the commissure between the left and right cusps of the aortic valve there was a small vegetation and another was present between the right and left posterior cusps. The left auricular appendage was not enlarged but the communication with the left auricle was difficult to trace because of edema about the ostium. The ostium permitted a probe to enter.

Spleen. The spleen weighed 480 Gm. The capsule was roughened by the adhesions mentioned above and in the capsule there were diffuse areas of thickening which appeared white and opaque. On the cut

surface the follicles were prominent and the pulp did not scrape.

Liver. The liver weighed 2,350 gm. The capsule had areas of roughening corresponding to the adhesions mentioned above. On cut surface the lobular markings were indistinct but in places were discernible. The *gallbladder* and *pancreas* were normal.

Adrenals. The periadrenal tissue was markedly edematous. The adrenals together weighed 25 Gm. On cut surface there was a normal proportion of cortex and medulla.

Gastro-intestinal Tract. The gastrointestinal tract and the mesentery were edematous. There were a few small hemorrhages in the middle third of the jejunum. The mesenteric lymph nodes were prominent but not much enlarged.

Genito-urinary Tract. Both kidneys were of equal size and together weighed 400 Gm. There was marked edema of the perirenal tissue. The capsule stripped with moderate ease revealing a surface which was mottled with deep brown and yellow areas. The brownish area appeared to be slightly depressed. A few hemorrhages, slightly larger than a pinpoint, were present and numerous small hemorrhages were seen in the capsule. On cut section the cortical markings were discernible, but with difficulty. The periureteral tissue was markedly edematous. The ureters were patent throughout and not dilated.

The *bladder*, *seminal vesicles*, *prostate* and *testicles* were normal.

MICROSCOPIC

Heart (Posterior Mitral Valve); Pericardium. Pericardium was thickened and edematous. There was an increase in supporting connective tissue and a considerable portion of the collagen was intensely eosinophilic. There were numerous monocytic cells with basophilic cytoplasm; some had a nucleus resembling that of a myocyte.

Myocardium. There was separation of

muscle fibers with a fine fibrillar connective tissue between them. Muscle bundles often were separated by a dense thick straight fibrous tissue, which was densely eosinophilic. This was also present, though more irregular, in perivascular zones. Occasional areas showed loss of muscle fibers and here and there were collections of polys, monocytic and fibroblastic cells. A considerable quantity of eosinophilic collagen was present in the region of the mitral ring.

Endocardium. The endocardium was thickened and vascularized and contained numerous macrophages with iron pigment as well as monocytic cells with eosinophilic cytoplasm, fibroblasts and an occasional multinucleated cell. The chordae tendinae were fused in the endocardial reaction.

Mitral Valve. The mitral valve was vascularized throughout the length of the auricular portion and much of the collagen was intensely eosinophilic.

Right Ventricle. The myocardium showed more pronounced intermuscular changes than in the MVP section. The endocardium showed more fibrosis and thickening, but in addition there was an acute mural vegetation composed of slightly basophilic irregular homogeneous material which resembled somewhat the collagen changes in the myocardium. In the meshes were red cells, delicate fibrillar reticulin, and occasional vacuolated cells. A chorda tendinae here also was fused in the endocardial change. The older endocardial changes extended into the septa between the myocardial fibres. There were blood vessels with the muscle fibres swollen and vacuolated with marked narrowing to almost complete occlusion of the lumen. There were bluish bodies in some of the capillary lumina which appeared like basophilic bodies described in the mural lesions of Lupus Erythematosus. In some sections, focal collections of polys and edematous blood vessel walls were found.

Lung. There was considerable congestion and scattered collections of mononuclear and septal cells containing pigment in the alveoli. In some areas the alveoli were filled with red blood cells and edema fluid as well as a few mononuclear cells and polys. In places the blood was hemolyzed. There were a few groups of alveoli and an occasional bronchiole filled with polys and mononuclear cells. A few small areas of atelectasis were also seen. In some places the alveolar septa were thickened. Occasionally, a larger vessel showed an eosinophilic wall. One large vein contained nuclear débris in the wall and thrombus. Other veins showed a similar change without thrombus. Sections of the subpleural abscess showed little inflammatory reaction around it. At its periphery was a moderate sized vein with a recanalized lumen. The visceral pleura was thick and edematous containing a few round and plasma cells. One localized collection of polys and mononuclear cells was seen in it. The parietal pleura was hypervascular and edematous. The collagen was swollen. There were scattered mononuclear cells with basophilic cytoplasm, and focal collections of round cells. The collagen of some of the vessels and perivascular areas appeared swollen. In these regions monocytic cells were present.

Diaphragm. There was marked edema and a few round and plasma cells were present. In addition, there were a number of mononuclear cells with basophilic cytoplasm. These were scattered through the tissue but were concentrated near the pleural surfaces. The collagen in the subserosal and perivascular areas was swollen.

Liver. The architecture was not disturbed. In places the capsule was thick and edematous and contained a few round and plasma cells. The portal veins were dilated. In the portal areas there were vacuoles in the liver cells.

Gallbladder. There were thickened arteries and autolysis.

Spleen. The capsule was thickened. The sinusoids were distended with blood and in places the pulp was hemorrhagic. There was periarteriolar fibrosis in the follicles. The septa were prominent. There was a calcific fibrotic nodule close to the capsule. A few collections of lipid laden cells were seen in the pulp, with considerable numbers subcapsular in location.

Pancreas. There was a rare focus of atrophy with collections of mononuclear cells and histiocytes. In places the capsular and septal collagen appeared swollen.

Small Intestine. The serosa was edematous and contained mononuclear cells. The arterioles were thickened, particularly in the submucosa. Some of these were hyalinized.

Adrenal. The periadrenal tissues were edematous. The capsule was thickened. The collagen was swollen. Focal cortical areas contained considerable lipid.

Kidney. Numerous glomeruli showed "hyaline thrombi" in the tuft. "Wire loop" lesions were not numerous. The cells of some of the tufts had considerable cytoplasm which seemed to occlude the lumen, rendering the glomerulus anemic. Some of the cortical arterioles contained thrombi. One medium sized vein contained a thrombus. The tubules contained granular material and a few contained hyalin casts. Here and there was a focal collection of mononuclear cells.

Prostate. An occasional artery was edematous.

Testicle. Spermatogenesis was active but few mature spermatozoa were seen. There was an increase in the interstitial cells.

Muscle. Sections of voluntary muscle revealed pronounced atrophy, degenerative changes and necrosis of the muscle fibers. Some of the fibers were multinucleated. There were focal areas containing mono-

nuclear cells and cells resembling endomysial cells. There was considerable amounts of fine fibrillar reticulin between the muscle fibers. Areas of fibrosis were present.

Lymph Nodes. The general architecture was not disturbed. Here and there the sinusoidal walls were thick and hyalin and occasionally a small artery contained a "hyalin thrombus." There were several areas in which there were groups of slightly basophilic large "hyalin" material, apparently in dilated sinusoids and surrounded by areas of necrosis. There were other areas of necrosis and a few areas containing polys. Macrophages with nuclear debris and red cells were present, usually about the necrotic lesions. About some nodes the tissue showed changes similar to those in the periadrenal tissue.

SUMMARY

A case of lupus erythematosus disseminatus in a male with a clinical course of approximately seventeen months was reported.

The onset was with polyarthralgia, "Erythema Multiforme," pleural and pericardial involvement. Later a butterfly rash developed. The patient was intermittently febrile. Late in the course he developed a systolic murmur and gallop rhythm. Renal involvement appeared clinically in the thirteenth month of the disease.

Autopsy revealed thickened serous surfaces, small endocardial vegetations of the Libman-Sacks type, collagen changes throughout the body involving blood vessels, muscles, serous membranes and endocardium. Kidney sections revealed "hyalin thrombi" with a few "wire loop" lesions of the glomeruli.

Purulent Pericardial Effusion

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MASSIVE purulent pericardial effusion is of sufficient clinical and academic interest to warrant the following case report:

A forty-six-year old white male was admitted to the Knickerbocker Hospital Medical Ward on October 9, 1944, complaining of fever, diffuse aches, non-productive cough and chills of five days' duration. The history revealed excessive alcoholism for about fifteen years, together with a diet lacking sufficient meats and greens. The physical examination upon admission disclosed herpes of the lips and a furry tongue having red, atrophic margins. A few crepitant râles were heard over the right lower lobe in the paravertebral area. The heart sounds, size and rhythm were normal. Blood pressure was 122/80, pulse 100 per minute. The liver was enlarged to two fingerbreadths below the costal margin. No spleen was palpable. The skin was hot and dry. The body hair was sparse. A few facial telangiectases were noted. The nail beds were cyanosed. There was no jaundice. The laboratory data upon admission included: temperature 103°F., red blood count 4.7 million, hemoglobin 14.5 Gm., 100 per cent, white blood count 21,000 with 96 per cent polymorphonuclears, and 4 per cent lymphocytes. Urinalysis revealed specific gravity 1.030, acid, albumin 2 plus, sugar negative, with occasional fine granular casts. An x-ray of the chest on the day of admission revealed "no evidence of any pulmonary infiltration or consolidation. The heart is within normal limits of size and configuration." The admitting diagnosis was right lower lobe pneumonia, and chronic alcoholism with liver cirrhosis and avitaminosis.

From Figure 1 depicting the course, it may be noted that 22 Gm. of sulfadiazine administered during the first four days had no appreciable effect on the sustained fever. Penicillin,

20,000 units every three hours, was then given for the next nine days, the total dose amounting to 900,000 Oxford units. Sulfadiazine to a total of 76 Gm. was continued at the same time until the fourteenth day; 3,000 cc. of 5 per cent glucose in normal saline was administered intravenously on the fourth day. Thiamine chloride in doses of 100 mg. was given by vein on the third and fourth day, then resumed on the fourteenth day and repeated daily thereafter. On the fifth day the second chest x-ray showed "no pulmonary change" but the heart shadow appeared slightly enlarged. Clinically, the patient claimed to be feeling better but objectively he appeared acutely ill and drowsy. Repeated chest films (Fig. 2) on the eleventh, fifteenth, eighteenth, and twenty-fourth days showed progressive increase in the size of the heart shadow. Electrocardiograms (Fig. 3) on the sixteenth and twenty-second days showed changes consistent with pericardial effusion. On the thirteenth day pericardial paracentesis yielded about 15 cc. of a serosanguineous fluid. On the fourteenth day large doses of aspirin were given in an effort to lower the temperature. The signs in the lungs seemed to clear entirely. The heart sounds continued to be good with no pericardial rub, gallop or murmurs audible. The blood pressure remained about 140/80 on the day of the pericardial tapping. On the twentieth day there appeared a persistent systolic blowing murmur at the apex. On the thirteenth day the patient continued to claim "improvement" although he appeared weaker and the skin showed increasing pallor. The apical murmur persisted but no pericardial rub or petechiae were noted. The circulation time was normal (18 seconds) on the seventeenth day. A transfusion, 500 cc. of whole blood, was given on the thirty-first day, the red blood count having dropped to 3.65 million and the hemoglobin to 71 per cent, 10.2 Gm. On the thirty-third day

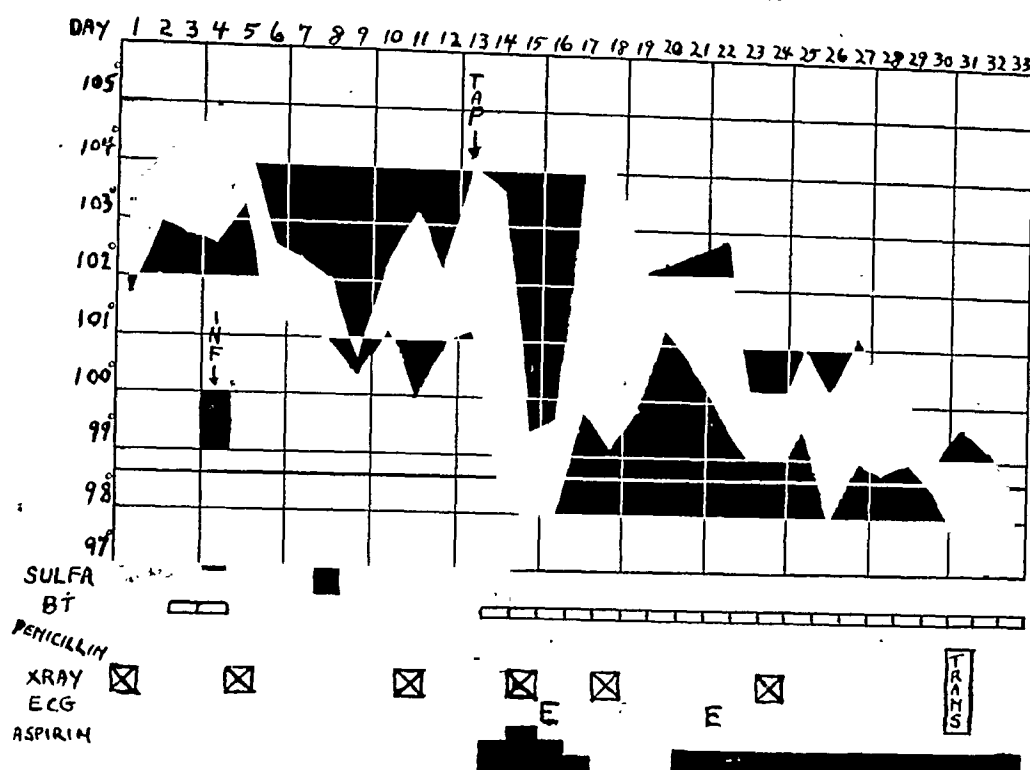
Pericardial Effusion—*Texon*

FIG. 1. Chart depicting the course of the disease.

the patient expired having become progressively more cyanotic with a rapid, thready pulse and muffled, indistinct heart sounds.

Additional data included negative Kahn and Kline tests. The pericardial fluid revealed 300,000 red blood cells per c. mm., 3,400 white blood cells per c. mm., (all lymphocytes). The smear revealed no organisms. Culture produced hemolytic staphylococcus aureus. Postmortem cultures from the pericardial effusion produced hemolytic streptococci, hemolytic bacillus coli and pneumococci type VII.

The necropsy performed by Dr. Joseph Balinger revealed the following: The heart is approached through an abdominal incision so that the shape and size are not discernible. The pericardial sac is markedly distended with turbid seropurulent fluid of moderate viscosity, measuring 1,500 cc. in volume. In two places the two layers of the pericardium are firmly and densely adherent. One of these is at the apex and adjacent left lateral border over an area 5 by 6 cm., the other layer over the anterior septum occupied an area 3 by 1.5 cm. These adhesions are inseparably attached and represent an old process. Elsewhere the pericardial sac is filled with the above described fluid. The two internal surfaces of the pericardium are covered with a mass of shaggy, fibrinous, tannish-brown, fri-

able adhesions measuring up to 1 cm. in thickness. In one focus along the posterior wall of the left ventricle, directly above the apex, there is a 1 by 1 cm. cheesy abscess directly above the myocardium and beneath the epicardium. The myocardium is flabby, pale, tannish-grey in color, parboiled in appearance, and measures 9 mm. at its thickest portion of the left ventricle and 2 to 3 mm. in the right ventricle. The endocardial surface of the chambers of the heart are pale, smooth, glistening and free from change. All orifices are normally patent, and all valves, save for the aortic, are free from gross change. The aortic valve presents a marked fusion of all its commissures in places measuring up to 1 cm. at the point of fusion. The cusps are slightly thickened and their free edges slightly rolled. There are no verrucae on any of the cusps. Instead there is a single, soft, pink, smooth, fleshy vegetation 7 by 5 by 5 mm. on the ventricular surface of the commissural junction between the right and left cusps. There is no surrounding or underlying ulceration of the cusps. The foramen ovale and ductus arteriosus are obliterated. The coronary ostia and their arteries are everywhere smooth, glistening and widely patent. The vena cavae are grossly normal.



FIG. 2. A to F, x-ray films show progressive increase in the size of heart shadow.

Microscopically, the fibers are somewhat swollen by the moderately severe parenchymatous degenerative changes. The epicardial surface is fibrously thickened and covered with a thick coat of inflammatory reaction, the base of which is already densely fibrous and vascularized (non-specific chronic granulation tissue). The uppermost layers of the coat are composed of an acute fibrinopurulent exudate. Plasma cells and phagocytosed blood pigment are noted in the deeper fibrosed portion of the epicardial coat. No evidence of tuberculosis is seen. The grossly described cheesy abscess in the subpericardial zone represents a purulent non-specific abscess showing early walling off by granulation tissue in which there are a few non-specific multinucleated giant cells.

There is no evidence of consolidation, infarction or hemorrhage in any portion of the lung.

There is marked distention and engorgement of the central veins and sinusoids of the liver with early fatty metamorphosis of the peripheral zone of hepatic cells. Grossly the liver weighed 2,260 Gm. The external surface is smooth, glistening and brownish tan. The organ cuts with normal resistance to present a nutmeg appearance of reddish-brown areas surrounded by paler tan areas representing passive congestion. The remainder of the organs revealed no unusual changes.

The final diagnosis was massive serofibrinopurulent pericardial effusion; congenital or rheumatic commissural fusion of the aortic

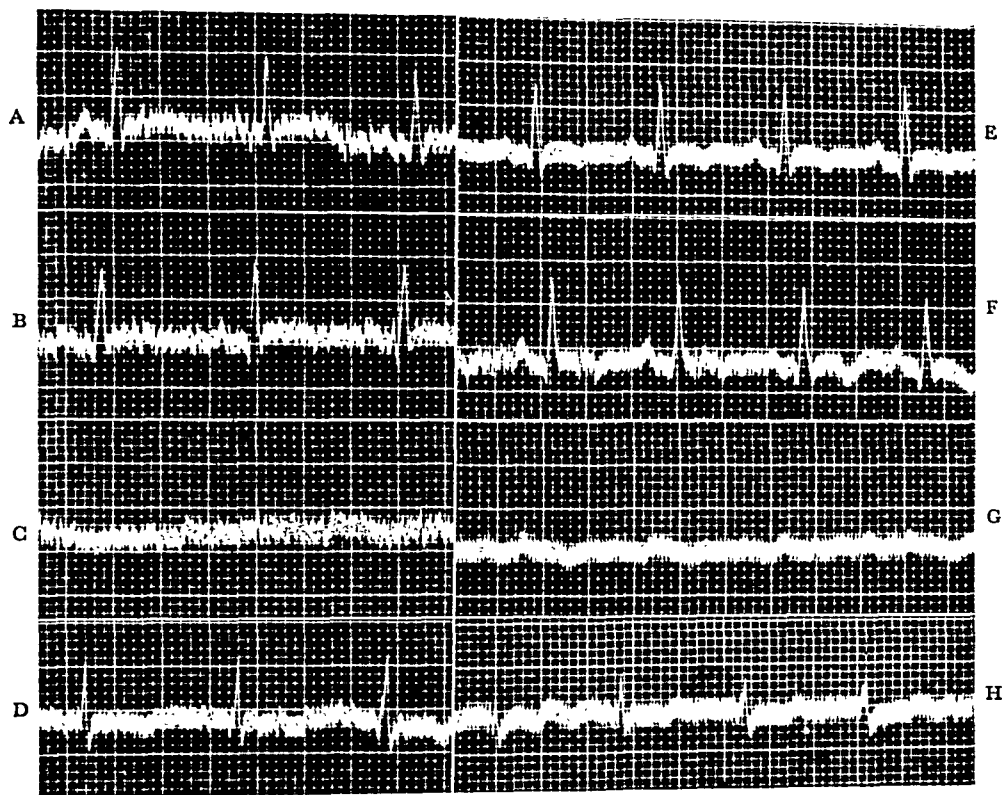


FIG. 3. A to H, electrocardiograms show changes consistent with pericardial effusion.

cusps, with superimposed recent vegetation (thrombotic, non-bacterial, vegetative endocarditis); and chronic passive congestion of the liver.

COMMENTS

The diagnosis of pneumonia upon admission was justified clinically although not visualized by x-ray. This may have been due to a retrocardiac position of the process. The involvement of the pericardium must be presumed to have occurred by contiguity. The therapy might have included penicillin instilled directly into the pericardial sac. The incidental finding at

necropsy of a rheumatic heart with aortic valvular involvement and vegetation again points out the frequency with which this occurs without obvious clinical signs or symptoms. It is believed that the cause of death was toxemia from the massive purulent pericardial effusion. Also, the patient, an alcoholic, did not resist the infection with normal constitutional powers.

SUMMARY

A fatal case of purulent pericardial effusion in which the patient was treated with sulfadiazine and penicillin is presented.

Vivax Malaria and the 8-Aminoquinolines

SHOULD it happen, as now seems likely, that generally useful curative agents for vivax malaria are contained in the series of 8-aminoquinolines, this will make an interesting chapter in the development of chemotherapeutic agents. Pamaquine was first used in the late 1920's and early 1930's on a very extensive scale. It was said, on the basis of these early studies, to possess some *suppressive* activity, as evidenced by its effect upon the erythrocytic phase of vivax malaria, as well as *curative* activity in this disease. It was also said to have little or no *suppressive* activity in falciparum malaria but a dramatic effect upon the gametocytes of the plasmodium responsible for this infection. In addition, it was said to have a true *prophylactic* action in each infection.

Shortly after the drug was available for large scale experimental use, it became apparent that the dosage recommended in the earlier studies could be expected to produce widespread and seriously toxic effects. However, the extent of the toxicity was not appreciated at a sufficiently early date to prevent the organization of reasonably well controlled trials to assay the *curative* action of pamaquine in vivax malaria.

It was common practice at that time, i.e., around 1930, to treat both vivax and falciparum malaria with full therapeutic doses of quinine, about 2.0 Gm. daily, for some fourteen to twenty-eight days. Consequently, when pamaquine was tested it was also administered for this period of time. It was demonstrated quite early that a combination of concurrently administered pamaquine and quinine is superior to the administration of either drug alone. For

example, in one series there was observed 75 per cent relapses in an eight-week period with quinine alone, 25 per cent with pamaquine alone and essentially none with a combination of the two antimalarials. The dosage of pamaquine in these studies, calculated as the hydrochloride, was as low as 40 mg. daily in some patients. It is possible that such a dosage regimen would have come into general use despite the toxic effects of the pamaquine except for the discovery and limited exploration of quinacrine which occurred about this time.

It was found that little advantage is derived from the administration of quinacrine beyond a seven-day period of treatment at 0.1 Gm. three times a day in population groups having a fair degree of immunity. As a reaction to this finding, it was thought that the course of quinine therapy might also be shortened with advantage. This belief, together with a growing appreciation of the toxic hazard of pamaquine, led to a curtailment in the duration of the administration of quinine and a lowering of the pamaquine dosage commonly used. It is not surprising, then, that the publications of the League of Nations recommended that combination pamaquine and quinine therapy be limited to seven days with the daily dose of pamaquine no higher than 30 mg. of the hydrochloride daily. The increase in the toxicity of pamaquine when administered concurrently with quinacrine led to the adoption of a convention whereby pamaquine was administered in similar dosage but for only five days and separated from quinacrine administration by a three-day drug-free interval.

It is now known that pamaquine admin-

istered at such a dosage and in such a manner has little to offer as a curative agent in many vivax malarias although it is a highly effective gametocidal agent. It seems likely that the early studies with pamaquine produced a different therapeutic result because the dosage was usually higher, administration was for a longer period of time, and the drug was administered concurrently with quinine. However, all three features were lost sight of in the years between 1931 and 1941 so that the early recommendations for the use of pamaquine by the services were not of the type that would be expected to yield a significant proportion of cures.

The study of pamaquine in the O.S.R.D. program involved, first, the demonstration that it does possess a truly prophylactic action, as previously defined, in both vivax and falciparum malaria. It was then shown that of the manifestations of pamaquine intoxication, which had been described, only the acute hemolytic anemias were of serious consequence and these do not occur or are rare in the white individual. This having been established, the further study of pamaquine and related substances was limited to this type of patient. It was then demonstrated beyond doubt that pamaquine does have a *curative* action when administered concurrently with quinine for fourteen days in vivax malaria due to either domestic or southwest Pacific strains. Having confirmed these essential facts relating to the antimalarial activity of pamaquine, it was further demonstrated that *prophylactic* and *curative* activity are characteristics of a class of compounds, i.e., derivatives of 6-methoxy-8-aminoquinoline, and not of only one member of the class.

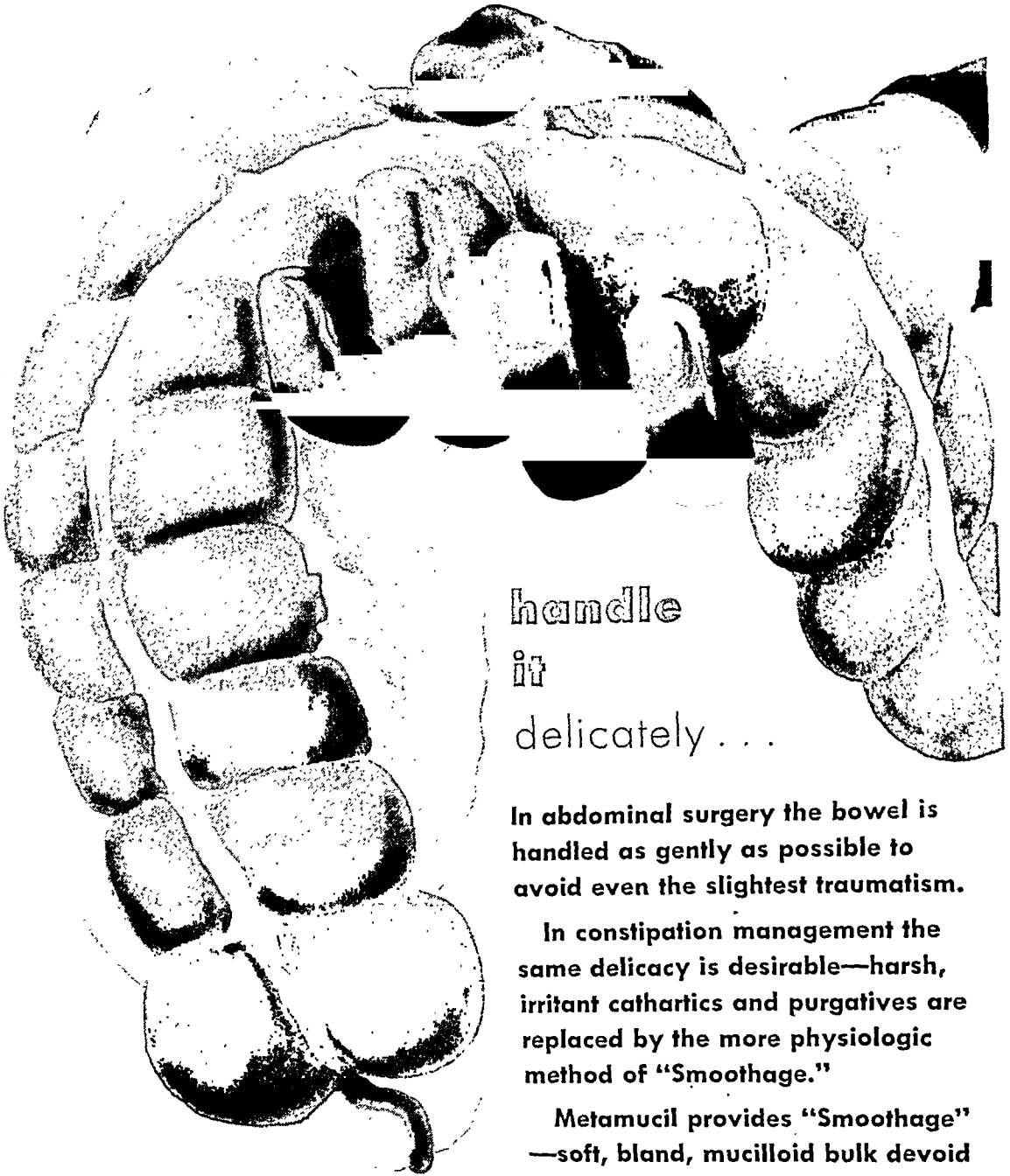
A systematic survey of 8-aminoquinolines for curative action in vivax malaria was then organized in a fashion which permitted the screening of a relatively large number of compounds with safety and with a fair chance of selecting any very promising

compound. It was assumed on the basis of the evidence then available that: (1) the maximal tolerated daily dose of pamaquine, when given in conjunction with quinine, is in the order of 90 mg. of pamaquine base; (2) since pamaquine produces symptoms of intoxication with daily doses of 30 mg. of base, or one-third the maximal tolerated dose, a generally useful 8-aminoquinoline would have to be effective at one-sixth the maximally tolerated dose; (3) one could predict the maximal tolerated dose of an 8-aminoquinoline in the human within a factor of two on a limited series of toxicity studies in the monkey; (4) it was possible to screen out, in toxicity studies in the monkey, compounds producing the irreversible type of central nervous system damage which characterizes plasmocide toxicity.

On the basis of these assumptions, 8-aminoquinolines were selected for clinical trial if they did not possess the plasmocide type of toxicity and if they were no more toxic than pamaquine. They were tested in combination with quinine in mosquito-induced Chesson vivax malaria at a daily dosage of one-sixth their calculated maximal tolerated dose. Combined drug administration was for fourteen days in all cases.

Studies of this general type were conducted during the last year of the O.S.R.D. program and are continuing in the present U.S.P.H.S. program. This much can be said with certainty. Pamaquine is not the best 8-aminoquinoline for use in the cure of vivax malaria. Pentaquine, 8-(5-isopropyl-aminoamyl-amino)-6-methoxyquinoline, is a superior drug for this purpose and probably generally usable if moderate precautions are taken.¹ However, whether it is the best which will be developed in the series is less certain.—JAMES A. SHANNON, M.D.

¹ LOEB, R. F., Chairman of Board for Coordination of Malarial Studies. Activity of a new antimalarial agent, Pentaquine (SN 13,276). *J. A. M. A.*, 132: 6, 1946.



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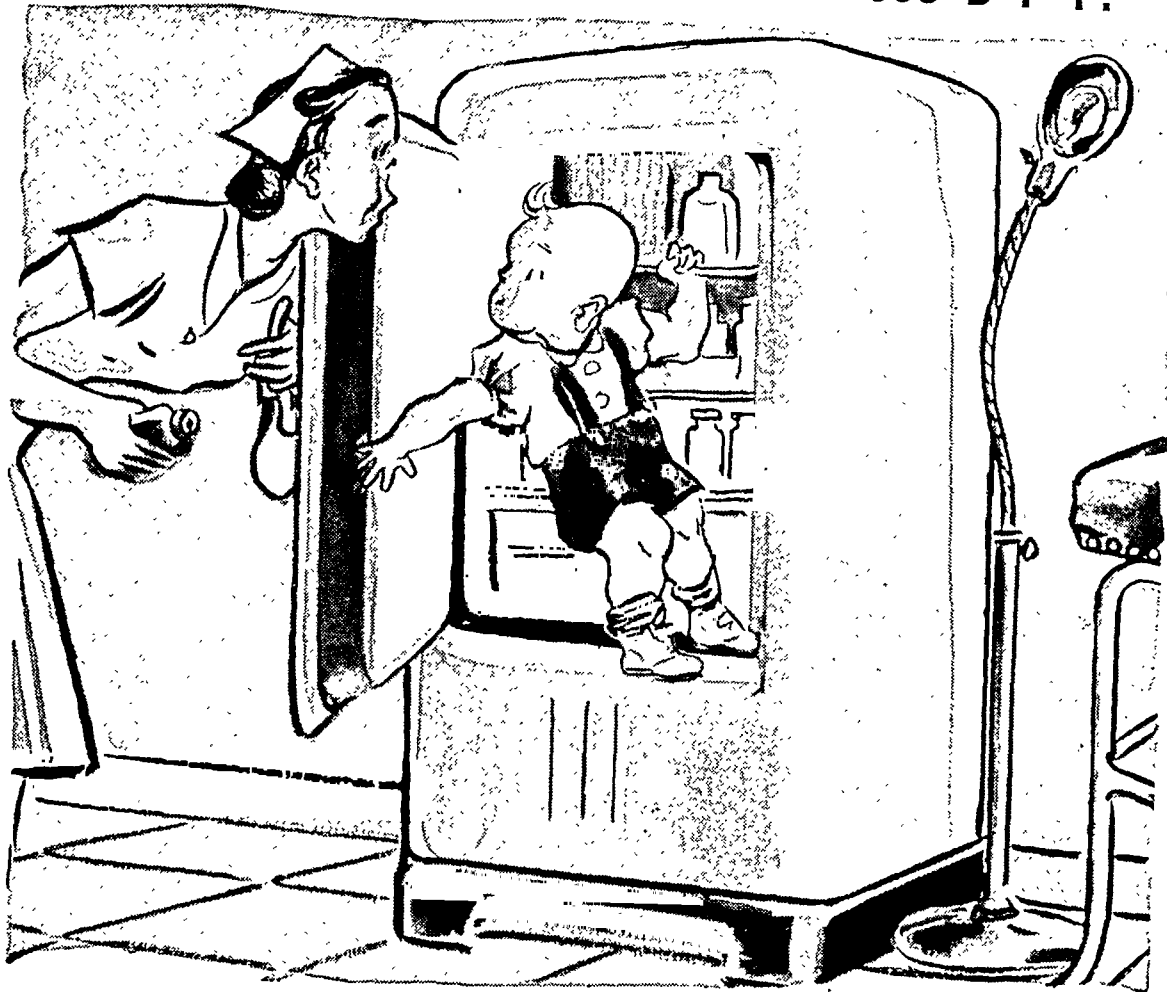
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1. J.A.M.A. 129:1080, Dec. 15, 1945
2. Illinois M. J. 88:85, August, 1945



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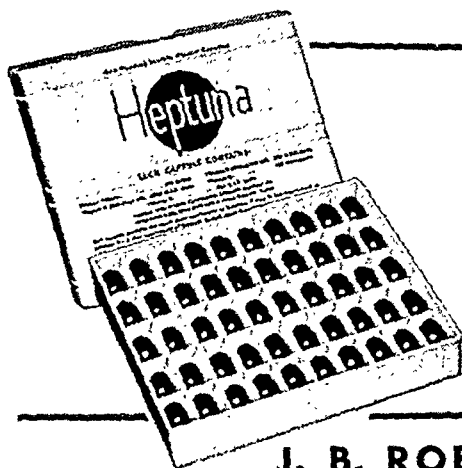
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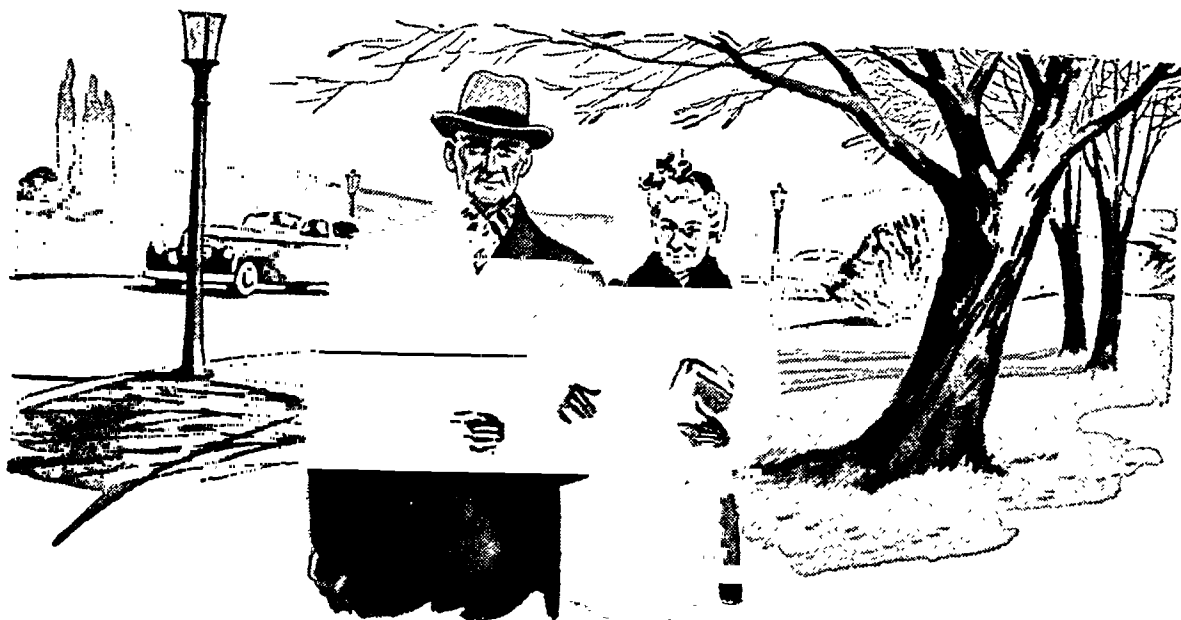
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The many somatic and emotional changes encountered in senescence are manifested in a variety of ways, especially by a decrease in appetite. Reduced energy expenditure, atrophic gastric changes, exaggerated food dislikes, and food intolerance all contribute, and not infrequently lead to a state of undernutrition. In older patients, this chain of events can easily produce excessive weakness and impaired stamina, adding to the burdens of senility.

Ovaltine proves an excellent means of preventing these complications. Its wealth of essential nutrients, as indicated by the table of composition, aids in preventing malnutrition. Made with milk as directed, Ovaltine is a delicious food drink. Older patients enjoy it as a mealtime and between-meal beverage, and especially as a bedtime drink. Its low curd tension assures easy digestibility and rapid gastric emptying, hence appetite is not impaired.

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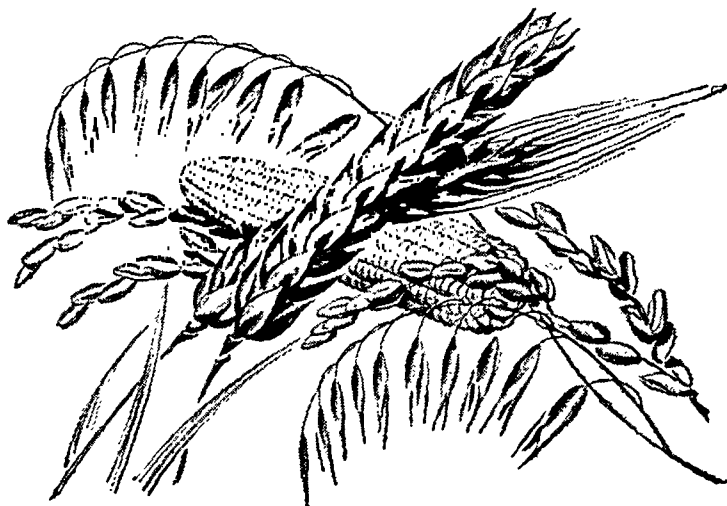


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½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

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CARBOHYDRATE	64.8 Gm.	NIACIN	6.81 mg.
CALCIUM	1.12 Gm.	VITAMIN C	39.6 mg.
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* Based on average reported values for milk.



Breakfast and the Daily Protein Need

The significance of breakfast in the satisfaction of nutritional requirements has been emphasized in many quarters in the recent past. Breakfast serves to replenish many nutrient stores depleted during the long fast from the previous evening meal, and provides the organism with caloric food energy needed for maximum efficiency during the morning hours. Hence nutrition authorities advise that breakfast should supply from one-fourth to one-third of the daily caloric and nutrient needs.

The morning meal should provide, among other things, its share of the daily protein requirement, since the protein needs must be met daily for proper growth of children and for good nutritional health of adults. In a basic breakfast so widely recommended—fruit, cereal, milk, bread and butter—the protein contribution is significantly high—20.7 Gm., or about 29 per cent of the adult requirement. Not a small amount of this protein is provided by the average serving of cereal (ready to eat or to be cooked), milk and sugar—fully 10 per cent of the adult daily protein need. Thus an important protein con-

tribution is made by the basic breakfast, of which cereals are an integral and universally recommended component.

This average cereal serving also provides B complex vitamins, caloric food energy, and important minerals. Its mixture of proteins is of high biologic value, applicable for the satisfaction of growth and maintenance requirements. Note from the table of composite averages the contribution made by the cereal serving—1 ounce of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar—and by the basic breakfast.

	Nutrition Composition of The Basic Breakfast*	Average represented by: cereal, 1 oz.; whole milk, 4 oz.; sugar, 1 teaspoonful
Calories	611	202
Protein	20.7 Gm.	7.1 Gm.
Fat	19.0 Gm.	5.0 Gm.
Carbohydrate	89.4 Gm.	33.0 Gm.
Calcium	0.465 Gm.	0.156 Gm.
Iron	3.0 mg.	1.6 mg.
Vitamin A	1074 I.U.	193 I.U.
Thiamine	0.52 mg.	0.17 mg.
Riboflavin	0.87 mg.	0.24 mg.
Niacin	2.3 mg.	1.4 mg.
Ascorbic Acid	64.8 mg.	

*Orange juice, 4 oz.; cereal, 1 oz.; milk, 4 oz.; sugar, 1 tsp.; bread (enriched, white), 2 slices; butter, 1 tsp. (5 Gm.); milk, 8 oz.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

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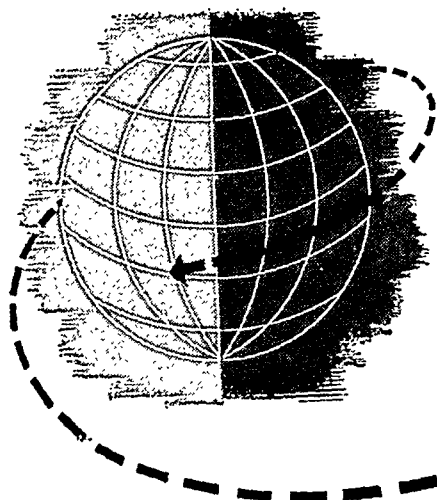
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Disabling myopathies may be the presenting feature in thyrotoxicosis. The authors discuss fully and instructively the various types of thyrotoxic myopathy, the occasional difficulties in diagnosis and the gratifying results of treatment of the underlying thyroid disease. Five illustrative cases of chronic thyrotoxic myopathy and two combining myasthenia gravis with thyrotoxicosis are presented in detail. Possible mechanisms are considered, with special reference to inadequate synthesis of creatine phosphate.

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Of The American Journal of Medicine, published monthly at New York, N. Y., for Oct. 1, 1946.

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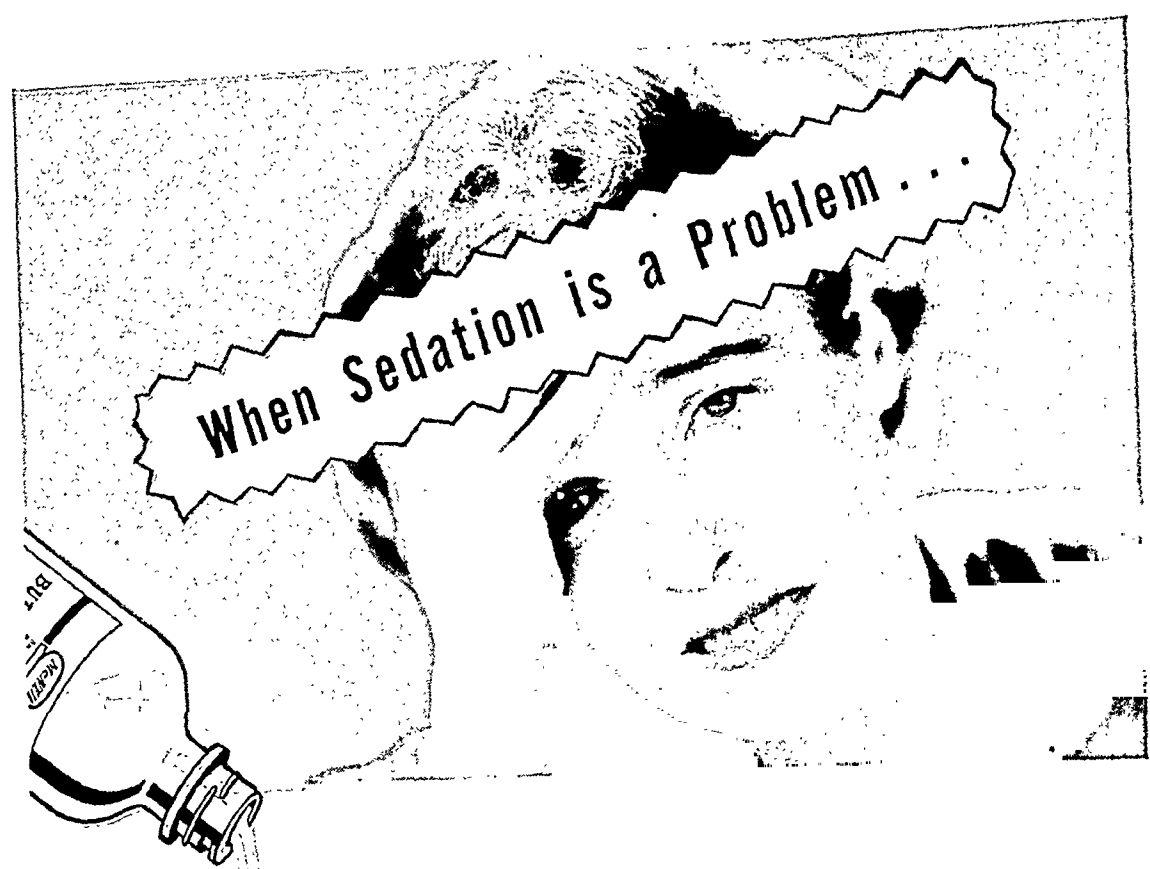
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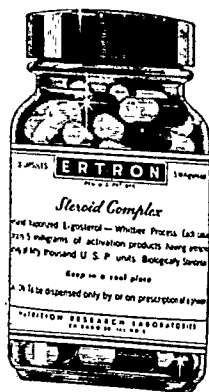
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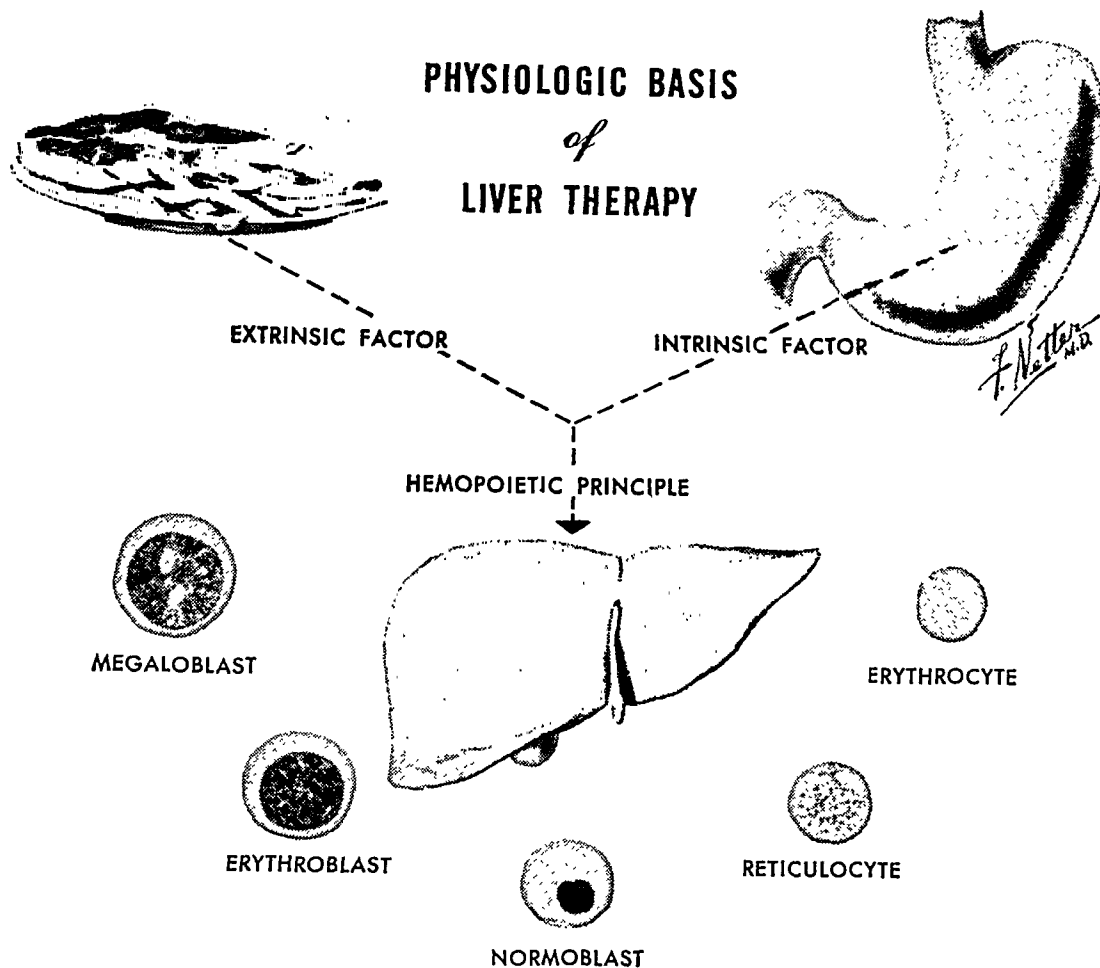
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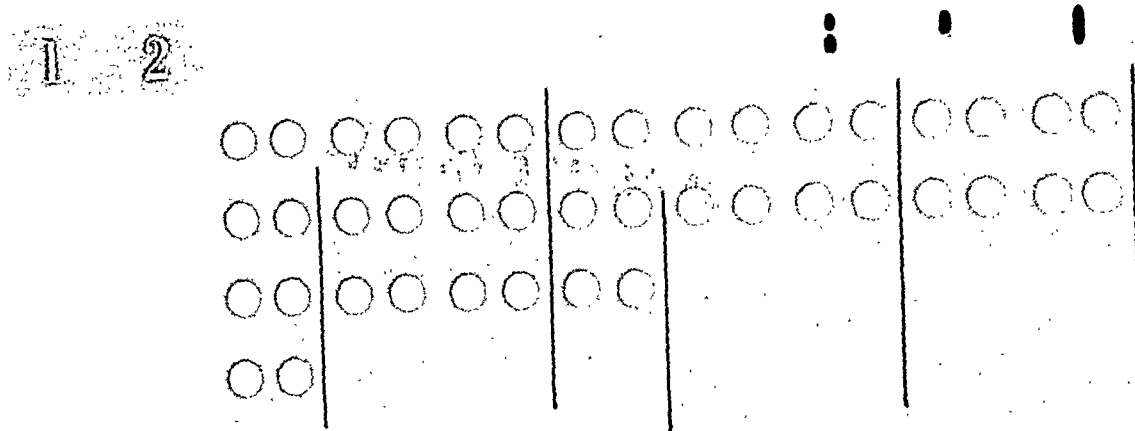
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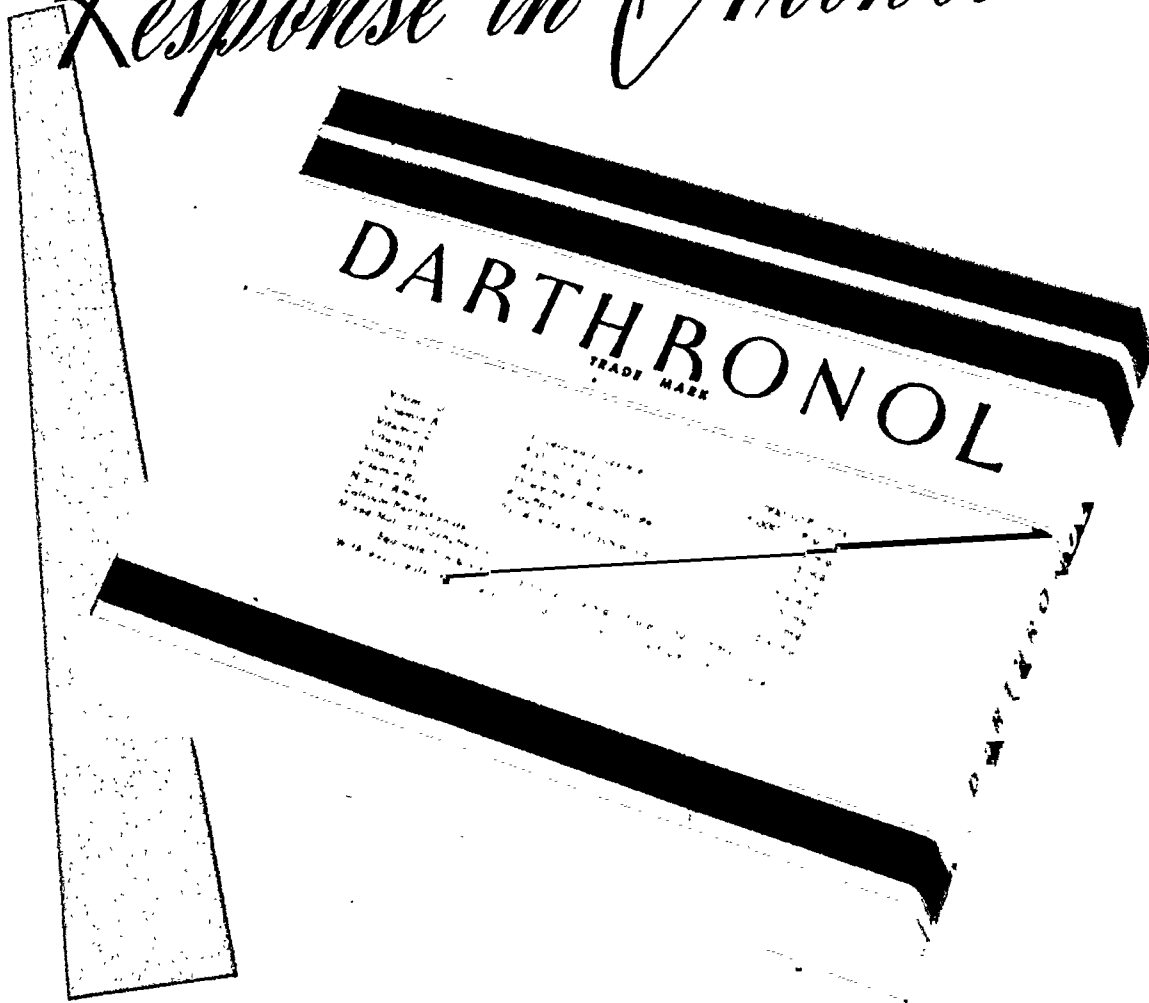
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The American Journal of Medicine

VOL. 1

DECEMBER, 1946 No. 6

Studies on Chronic Thyrotoxic Myopathy*

GEORGE W. THORN, M.D. and HOWARD A. EDER, M.D.

BOSTON, MASSACHUSETTS

MUSCULAR weakness is a common accompaniment of thyrotoxicosis, and it is well known that many patients with severe thyrotoxicosis manifest striking impairment in muscular function.¹ There are, in addition, patients with thyrotoxicosis in whom the signs and symptoms of muscular weakness may be entirely out of proportion to the degree of thyrotoxicosis. In some of these patients the usual clinical signs of thyrotoxicosis may be so slight or obscure as to be overlooked. These instances, although not common, merit consideration because of the striking improvement in muscular strength and development which may follow treatment of the underlying thyrotoxicosis.

Starling, Darke, Hunt and Brain² have suggested the following classification of myopathies associated with thyrotoxicosis: (1) Exophthalmic ophthalmoplegia; (2) thyrotoxic myopathy, (A) acute thyrotoxic myopathy, (B) chronic thyrotoxic myopathy, (C) thyrotoxic periodic paralysis; and (3) myasthenia gravis and thyrotoxicosis.

Exophthalmic ophthalmoplegia^{2,3} is a disorder localized in the soft tissues and muscles of the orbits. It frequently persists after thyroidectomy and in some instances actually progresses postoperatively. Recent studies by Rundle and Pochin⁴ suggest that the exophthalmos is due to an increased fat content of the retrobulbar tissues. Severe generalized muscular disease has rarely been noted in patients with this condition.²

Acute thyrotoxic myopathy as described by Heuer⁵ in 1916 appears to be a rapidly progressive myasthenia with involvement of the bulbar muscles as well as of the muscles of the limbs and trunk. It is usually fatal in one to two weeks, and death occurs most frequently from respiratory paralysis. In the case described by Heuer the differentiation from myasthenia gravis was made largely on the basis of response to faradic stimulation. It is questionable whether these cases represent a distinct entity rather than thyrotoxicosis associated with myasthenia gravis.

Thyrotoxic periodic paralysis not uncommonly occurs in conjunction with familial periodic paralysis. This condition should be distinguished from chronic thyrotoxic myopathy by the fact that patients are asymptomatic between attacks and their muscles appear to be normal. To date, thirty-five such cases have been described (Talbot⁶). In some instances thyroidectomy may cause a complete remission of symptoms (Dunlop and Kepler⁷), while in others there was merely a decrease in the frequency of attacks (Morrison and Levy⁸). The association of changes in serum potassium concentration with attacks of periodic paralysis is well known.⁹ The mechanism whereby excessive thyroid hormone affects the disease is not understood.

Chronic thyrotoxic myopathy is one of the most important muscular disturbances associated with hyperthyroidism. It is char-

* From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston, Mass.

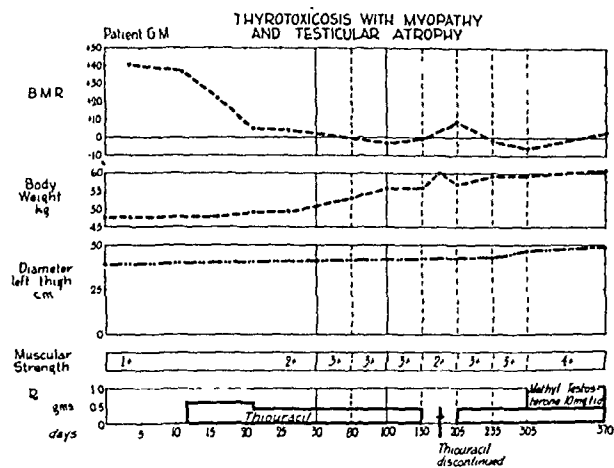


CHART 1.

acterized by marked muscular atrophy which is symmetrical and most frequently involves the shoulder and pelvic girdles. It was first described in 1895 by Bathurst.¹⁰ The literature has recently been summarized by McEachern and Ross¹¹ who have reported thirteen such cases including three of their own.

We wish to report five additional cases of this disease which were seen over a relatively short period at the Peter Bent Brigham Hospital and to emphasize the importance of recognizing these cases because of the dramatic improvement which may follow correction of the underlying thyrotoxicosis.

CASE REPORTS AND OBSERVATIONS

The principal features in the five cases of chronic thyrotoxic myopathy are summarized in Table I.

CASE I. A fifty-year old male presented generalized muscular weakness with striking atrophy of the muscles of the shoulder girdle. Signs of thyrotoxicosis were minimal; gonadal atrophy was present. The patient made an excellent response to thiouracil therapy supplemented later with methyl testosterone. (Chart 1.)

G. M., No. M65090, a fifty-year-old Italian mill worker, entered the Peter Bent Brigham Hospital on October 6, 1943, because of marked weakness. For thirty years the patient had tolerated warm weather poorly. He had always been comfortable in cold weather and frequently slept only with a sheet, even in cold weather. During the seven months before admission these

symptoms became more pronounced, and, in addition, he had noted marked muscular weakness, especially of his legs. For eight weeks this had been so pronounced that he had been unable to climb stairs and spent most of his time in bed. During this period he had noted rapid heart action, and ankle edema had occurred at the end of the day. He had lost approximately 30 pounds, and his appetite had not been as good as usual.

The patient's family history was non-contributory, and his past history was not noteworthy except for a marked decrease in potency.

Physical examination on admission showed a middle-aged, dark Italian lying quietly in bed with a slight amount of restlessness. His temperature was 98°F., pulse 104, respirations 16 and blood pressure 140/70 mm. Hg. His skin was warm but not moist except in the palms. There was marked muscular atrophy, especially in the muscles of the shoulder girdle with marked winging of the scapulae and marked atrophy of the supraspinatus and biceps muscles. There was also atrophy of the legs, especially of the quadriceps. Muscles of the forearms and lower legs did not show such marked atrophy. There was no fasciculation. His gait was unsteady; he walked with a broad base and was unable to climb stairs at all. He did not have exophthalmos or other eye signs. There was a definite fine tremor to the tongue and outstretched hands. The thyroid was enlarged but contained no nodules, and a bruit could be heard over it. The lungs were normal. The heart was not enlarged, the sounds were forceful, and there was a grade 1 systolic murmur at the apex. The abdomen was normal. The genitalia were small with small testes, and the prostate was also small. There was slight pitting edema of the ankles. Neurological examination showed nothing abnormal except the muscular weakness. Reflexes were physiological.

Laboratory examination revealed the following: Blood serology was negative. Urine specific gravity was 1.015 with no protein or sugar. Sediment contained many white cells. Hemoglobin was 12.2 Gm. per cent, hematocrit 35 per cent, and sedimentation rate 22 mm. per hour (method of Wintrobe). The white blood count was 8,250, and smear appeared normal.

TABLE I
THYROTOXIC MYOPATHY

Patient.....	G. M. Case I	M. S. Case II	E. M. Case III	J. B. Case IV	Y. C. Case V
Sex and age.....	Male, 50 years	Male, 40 years	Female, 43 years	Female, 56 years	Female, 22 years
Duration of symptoms.....	7 months	2 months	6 months	6 months	6 months
Thyroid enlargement.....	+	+	++	0	++
Eye signs.....	None	Lid lag	Stare, lid lag	None	Exophthalmos, stare, lid lag, impaired convergence
Tremor.....	+	+	++	0	+
Muscular involvement	Generalized weakness and atrophy, most marked in shoulder girdle	Generalized weakness with atrophy especially in arms	Generalized weakness and atrophy; regurgitation of fluids	Extreme generalized weakness and atrophy	Generalized weakness; atrophy especially in upper arm
Fasciculation.....	0	0	0	0	0
Initial basal metabolic rate—%..	+37	+40	+60	None taken	+33
Spontaneous creatinuria mg./24 hours.....	100	200	590	Not done	420
Creatine tolerance test*					
% retention of ingested creatine.....	62	28	Not done	Not done	Not done
Urinary 17-ketosteroids mg./24 hours.....	8.3	8.6	2.7	Not done	9.4
Cardiac enlargement by x-ray—%.....	0	0	+25	0	+10
Circulation time—seconds**.....	9	Not done	11	Not done	14
Prostigmine test..	No improvement	No improvement	No improvement	Not done	No improvement
Treatment.....	Thiouracil for 1 year; methyl testosterone for 2 months	Subtotal thyroidectomy; methyl testosterone; testosterone propionate for 4 months	Thiouracil for 9 months; thyroidectomy	Iodine for 2 days	Thiobarbital for 5 months
Result.....	Strength returned almost to normal	Strength returned to normal until onset of hypothyroidism	Strength returned almost to normal	Died	Good return of strength
Basal metabolic rate after treatment.....	−3% (18 months)	−22% (6 months)	+20% (18 days)	−3% (5 months)

* Normal for males 85–100% retention; normal for females 80–95% retention.

** Decholin, arm to tongue; normal 15–18 seconds.

Blood urea nitrogen was 11 mg. per cent, non-protein nitrogen 37 mg. per cent, total protein 6.2 Gm. per cent, albumin 4.0 Gm. per cent, globulin 2.2 Gm. per cent, fasting blood sugar 99 mg. per cent, blood cholesterol 175 mg. per cent, calcium 5.6 m.M. per liter, phosphorus

1.56 m.M. per liter, and alkaline phosphatase 3.7 Bodansky units. Stool examination was normal. Arm to tongue circulation time (decholin) was 9 seconds. Prostigmine test showed no increase in muscular strength after administration of 1.5 mg. of prostigmine subcutaneously.

weakness for two months. He had been in good health until six months prior to admission when he noted a choking sensation on swallowing with a sense of fullness in his epigastrium. On a regimen of atropine and aluminum hydroxide, these symptoms had subsided. Two months before admission he had begun to feel tired and noted weakness of his muscles with difficulty in walking. In the week prior to admission the slightest exertion had caused him to break out in a cold sweat with a generalized aching in his bones and muscles. During the previous month he had lost 18 pounds despite the fact that his appetite had been as good or better than before. In addition, he had noted some palpitation, nervousness, a tendency to sweat easily and a slight tremor of his hands. He had been placed on Lugol's solution by his local physician and had continued this up to four days prior to admission. The remainder of the patient's past history and his family history were non-contributory.

Physical examination on admission showed a well nourished, white male who was very restless and nervous. His temperature was 99°F., pulse 90, respirations 20 and blood pressure 130/80 mm. Hg. His weight was 64 kg. He showed generalized muscular weakness of a mild degree, somewhat greater in his right arm than in his left, with some loss of muscle substance on the right. His reflexes were normal. The skin was warm and of fine texture, and he was sweating freely. His hair was normal in distribution and appearance. The eyes were not unusually prominent, but there was slight lid lag. There was a fine tremor of the tongue. Thyroid was slightly enlarged with a slight bruit over the right lobe. The lungs were clear, the heart was not enlarged, and sounds were not hyperactive. There was a grade I systolic murmur at the apex. The abdomen was not remarkable and there was no significant tremor of the hands. His testes were small, and his prostate was soft.

Laboratory examination revealed the following: Blood serology was negative. Urine specific gravity was 1.012, no protein or sugar. Sediment was negative. Hemoglobin was 13.5 Gm. per cent, hematocrit 42 per cent, sedimentation rate 6 mm. per hour. White blood count was 9,000 with 58 per cent neutrophils and 38 per cent lymphocytes. The red cells appeared normal.

Blood urea nitrogen was 10 mg. per cent. Total protein was 6.3 Gm. per cent, albumin 3.2 Gm. per cent, globulin 3.1 Gm. per cent. Fasting blood sugar was 115 mg. per cent, carbon dioxide combining power 25.8 m.M. per liter, serum chloride 97 m.Eq. per liter, cholesterol 149 mg. per cent, urine 17-ketosteroids 8.6 mg. per twenty-four hours. The stool was normal. While on a creatine-free diet he excreted 0.201 Gm. of creatine in twenty-four hours. He retained only 28 per cent of the ingested creatine (2.6 Gm.) in the creatine tolerance test. The electrocardiogram showed normal curves and the chest film was normal. The gastrointestinal series was normal except for pylorospasm, and the barium enema was also normal. After 1.5 mg. of prostigmine subcutaneously, he showed no increase in muscular strength. His initial basal metabolic rate was +11 per cent.

During his hospital stay he ran a low-grade fever while on bed rest. (Chart 2.) His basal metabolic rate gradually rose from +11 to +40 per cent on his eleventh hospital day. (He had been on Lugol's solution before admission.) He was then placed on Lugol's solution and in six days his basal metabolic rate fell to +19 per cent, his creatine excretion dropped to 0.015 Gm. per twenty-four hours, and subtotal thyroidectomy was performed. The gland showed hyperplasia with iodine involution. After operation his basal metabolic rate continued to drop and was -14 per cent on June 10th, at the time of discharge from the hospital. After operation he had no spontaneous creatinuria, and he retained 84.4 per cent of the ingested creatine in the tolerance test. His strength rapidly increased. Before operation he could step up and down on the 12-inch step for only 50 seconds; after operation he was able to go for 88 seconds. One month after operation he was able to do this work for 150 seconds. After returning home his strength improved. He gained 10 kg. and was able to return to work. He continued in good health until October, 1943, when he began to feel fatigued and began to note slowness of action and thought. His basal metabolic rate fell to -20 per cent, and he was readmitted in November, 1943, with signs and symptoms of myxedema. His cholesterol at that time was 500 mg. per cent.

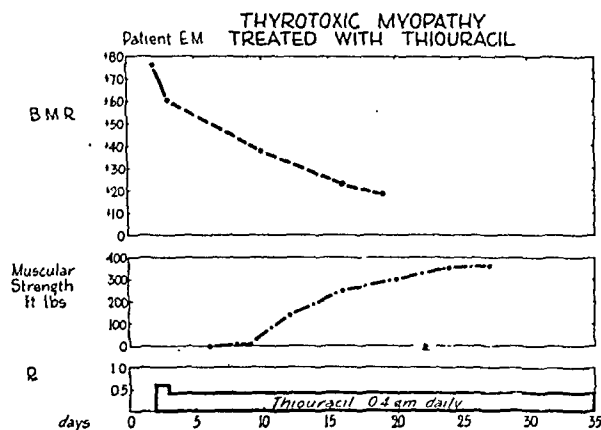


CHART 3.

Creatine tolerance test showed retention of 84 per cent of the ingested creatine. He was somewhat weaker and was able to raise himself on the 12-inch step for 90 seconds. He was started on 60 mg. of thyroid daily and has since lost his signs of myxedema.

After discharge he still complained of some muscular weakness although there was no evidence of atrophy. Since it had been noted that his testes were small, prostate soft, and libido was absent, he was started on 30 mg. of methyl testosterone daily. After one month he showed appreciable improvement and was able to work ten hours a day. The following month he received testosterone propionate 25 mg. daily for three days and bi-weekly thereafter. On this medication his strength returned completely to normal, and he was able to work on the step for 115 seconds.

CASE III. This was a forty-three-year-old female with extreme muscular weakness and generalized muscular atrophy. Signs of thyrotoxicosis were clearly evident. Treatment with thiouracil resulted in a prompt and striking improvement in muscular strength as well as in size of muscles. (Chart 3.)

E. M., No. M65818, a forty-three-year-old housewife, entered the Peter Bent Brigham Hospital on February 3, 1944, because of such extreme weakness that she had been unable to get out of bed for the previous three weeks. She had felt quite well until six months before admission when she had noted marked weakness of her arms and legs with fatigue after very slight exertion. This weakness had become progressively worse, and for several months she had been unable to climb stairs. For three

weeks she had been too weak to get out of bed, and she said that exertion made the weakness more marked. For several months her speech had been thick. There had been occasional regurgitation of fluids into her nose, but she had had no diplopia. She had always been uncomfortable in hot weather. Since her present illness, her appetite had been poor and she had lost 30 pounds. In addition, she had become nervous and irritable and had noted palpitation. Her local physician had told her that her heart was irregular but that she had no symptoms of heart failure. Four months previously she had noted swelling of her neck but had had no hoarseness or difficulty in swallowing. Her physician had prescribed iodine which had been followed by marked relief of symptoms, but this therapy had not been continued. The remainder of the patient's past history was non-contributory.

The family history was of interest in that she had one sister with a goiter of three years' duration.

Physical examination on admission showed an extremely thin woman with evidence of marked weight loss. Her temperature was 98.6°F., pulse 106, respirations 32, blood pressure 130/64 mm. Hg. She was very weak and could not sit up unsupported. The skin of her face had a pinkish hue; her palms were warm and moist; and there was marked wasting of all muscles. Her eyes were prominent with a definite stare and lid lag. Retinal vessels were normal. She had a marked tremor of the tongue. The thyroid was visibly enlarged in both lobes, and there was a definite bruit. It was not nodular. She had definite tremor of the outstretched hands. Her lungs were normal; her heart was slightly enlarged; the sounds were forceful. There was a grade 1 systolic bruit at the apex and base. The liver could be felt below the costal margin. She had no enlargement of the spleen or kidneys. Her reflexes were normal. She had marked hypotonia of her muscles. Her speech was thick, but it did not become worse on continuous effort.

Laboratory data revealed her blood serology to be normal. Urine specific gravity was 1.024 with no protein or sugar; sediment was clear. Hemoglobin was 12 Gm. per cent, hematocrit

43 per cent, sedimentation rate 7 mm. per hour. White blood count was 7,700 with 71 per cent neutrophils. The smear appeared normal. Blood urea nitrogen was 9 mg. per cent. Total protein was 5.4 Gm. per cent, albumin 2.7 Gm. per cent, globulin 2.7 Gm. per cent. Non-protein nitrogen was 29 mg. per cent. Fasting blood sugar was 96 mg. per cent. Serum cholesterol ranged between 128 and 242 mg. per cent. She excreted 0.59 Gm. of creatine in twenty-four hours. A throat culture showed *Streptococcus* (alpha) and *Staphylococcus aureus*. Circulation time was 11 seconds on admission (arm to tongue decholin). The chest film showed the heart to be 25 per cent above average. The lungs were clear, and there was no substernal thyroid. Bone films showed normal detail with no osteoporosis. An electrocardiogram showed auricular fibrillation with inverted T₄. Repeated electrocardiogram showed normal sinus rhythm with left axis deviation. Initial basal metabolic rates were +76 per cent and +60 per cent.

The patient was started on thiouracil 0.4 Gm. daily. (Chart 3.) On her fifth day of treatment her basal metabolic rate was +38 per cent. At that time she had her second attack of paroxysmal auricular fibrillation, the first being on the day of admission. She had normal sinus rhythm with sinus tachycardia at all other times. During her hospital stay her basal metabolic rate fell steadily until it was +20 per cent at the time of discharge. Her pulse rate decreased also and was 80 at the time of discharge, whereas it had been 110 on admission. Her circulation time (decholin) increased to 15 seconds.

The most striking changes, however, were in her strength. She was able to walk around, whereas on admission she could not even sit up in bed. Her muscle strength as tested by standard work showed a 64-fold increase. She was alert and wide awake. Her skin was less warm but she still had slight tremors. Her appetite improved markedly, although there was no weight gain. Her heart was regular; sounds were not especially forceful. The systolic murmur at the apex disappeared. The thyroid was slightly larger and more firm. The bruit was still present but was markedly diminished. She was discharged on her thirty-first hospital day to continue on thiouracil medication. When last

heard from after two and one-half months she had gained 9 kg. and was up and around and able to do most of her housework.

CASE IV. A fifty-six-year-old female with extreme weakness and generalized muscular atrophy, had practically no signs of thyrotoxicosis. Her progress in the hospital was rapidly downhill with death on the seventh hospital day. Pathological examination revealed hyperplasia of the thyroid, striking atrophy of the skeletal muscles and of the *glomerulosa* layer of the *adrenal cortex*.

J. B., No. M64553, a fifty-six-year-old colored housewife, was admitted to the Peter Bent Brigham Hospital on July 9, 1943, because of palpitation and progressive fatigability of three months' duration. For six months previous to admission it had been noted that the patient desired cool surroundings and preferred cold to hot weather. At that time she also had complained of generalized weakness. Later this had become so pronounced that even climbing a short flight of stairs had produced severe fatigue, compelling her to rest in a chair from five to fifteen minutes thereafter. Two months later, because of steadily increasing weakness, she had been forced to cease work as a dressmaker. At the same time she had noticed palpitation. She had been seen by her family physician who found a tachycardia of 110–128, and she had been slowly digitalized. Palpitation had persisted up to the time of admission. The weakness had gradually increased, and one week before admission it had become so severe that she had had to stay in bed all the time. Two days before admission, she had been so weak that she needed constant nursing attendance. She became dyspneic on the slightest exertion. Just prior to admission, it had been noted that her speech was thick and that she had difficulty in pronouncing her words. The patient had lost weight during this illness, but the exact amount was not known.

Her past history included an episode five years before admission of swelling, redness and tenderness of her left ankle and knee. A diagnosis of acute rheumatic fever had been made at that time. The family history was non-contributory.

Physical examination on admission revealed a drowsy colored woman showing evidence of marked weight loss. Her temperature was 100.6°F., pulse 108, respirations 22 and blood pressure 140/80 mm. Hg. She appeared lethargic and spoke in a slow lisping voice. In the middle of the interview she became dyspneic and exhausted and lapsed into sleep. Her skin was warm and dry. There was partial alopecia at the temples and frontal regions. There was no evidence of oculomotor weakness. The pupils were equal and reacted to light and accommodation. There was no exophthalmos or abnormal eye signs and the ocular fundi were normal. The tongue was coated, was not atrophic and was without fibrillary twitchings. Neck veins were not distended. The thyroid was small and palpable without an audible bruit. The lungs were emphysematous but without râles. The heart was not enlarged, and the rhythm was regular with many extrasystoles. There was a systolic murmur heard over the entire precordium, loudest at the base. The abdomen was normal. Extremities showed generalized muscle wasting, most marked in the forearms, hands, calves and feet. There were no fasciculations. There was marked muscular weakness. The patient was unable to hold her hands out in front of her for more than half a minute and was barely able to lift more than one leg off the bed at a time. The only reflexes obtained were hypoactive biceps and knee jerks.

Laboratory examination revealed the following: Urine was not remarkable except for a trace of protein. Blood serology was normal. Red blood count 5.0 million. Hemoglobin was 14.5 to 16.0 Gm. per cent, hematocrit 45 per cent, sedimentation rate 17 mm. per hour, white blood count 6,000 to 10,000 with 58 per cent neutrophils. Platelets were present in normal amounts; the smear appeared normal. Blood urea nitrogen was 13 mg. per cent and non-protein nitrogen was 20 mg. per cent. Total protein was 8.6 Gm. per cent with 3.4 Gm. per cent albumin. Fasting blood sugar was 117 mg. per cent, carbon dioxide combining power 30.8 m.M. per liter, serum chloride 100 m.Eq. per liter. Spinal fluid was clear and colorless. No cells were present, and the dynamics were normal. Hinton and gold sol were

negative. Electrocardiogram showed a sinus tachycardia with a ventricular rate of 120. There were premature auricular beats, left axis deviation, inverted T₁ and T₄ and a slightly elevated ST₄.

The patient ran a rapidly downhill course with a gradual rise of temperature, pulse and respiration rate. On the second day she was much more drowsy and the weakness was much more striking than on admission. She spoke with a thick voice and enunciation was poor. At no time, however, was there facial or hypoglossal paralysis. A chest film showed the heart to be normal in size and shape with some blunting of the left costophrenic angle. The heart beat was rapid and of small amplitude. On the fifth hospital day her temperature rose to 104.3°F., pulse to 100, respirations to 40. From this point on she was continuously stuporous, incontinent and required parenteral fluid administration. On the fifth day she also received 10 drops of Lugol's solution. The following day she received 1 Gm. of sodium iodide, 5 Gm. of sodium sulfadiazine, and 3 cat units of digitalis intravenously. This did not alter her course. Her temperature rose to 107.2, with a pulse of 168, and she died on her seventh hospital day.

Postmortem examination showed the thymus to be enlarged; it weighed 26 Gm. The heart weighed 340 Gm. and appeared normal. The abdominal viscera appeared normal except for a small argentaffinoma in the cecum, healed salpingo-oophoritis and a small leiomyoma of the uterus. The liver weighed 1,100 Gm. The kidneys were normal. The adrenals grossly were not remarkable. The thyroid weighed 40 Gm. and seemed to be slightly enlarged and nodular.

Microscopic examination showed moderate congestion of the sinusoids and central veins of the liver. The adrenal cortex (Fig. 1) appeared atrophied especially in the glomerulosa layer where the cells were decreased in number, and those remaining appeared small with pyknotic nuclei. The thyroid (Fig. 2) acini were lined with high columnar epithelium, and there were only small amounts of colloid in the acini. Some of the fibrous tissue septa between the acini contained large aggregations of densely packed lymphocytes. Striated muscle bundles (Fig. 3) appeared atrophic in many areas with fibrous

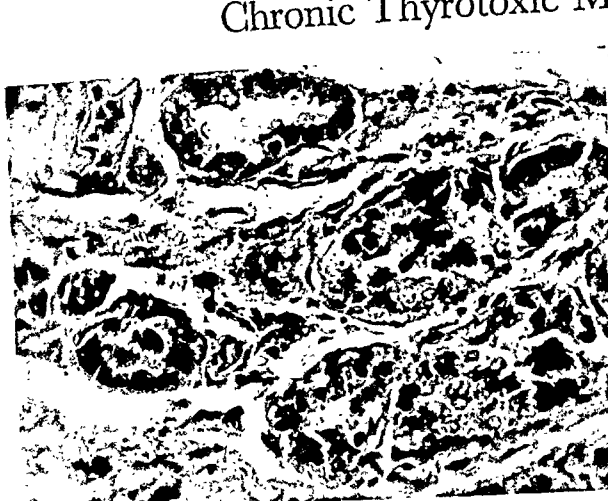


FIG. 1. Patient J. B.; thyroid; hyperplasia of epithelium high columnar cells; marked diminution in colloid content. E M B $\times 225$.



FIG. 2. Patient J. B.; adrenal cortex; atrophy of the zona glomerulosa. Cells are decreased in number and those remaining are small and have pyknotic nuclei. H and E $\times 450$.

replacement of muscle fibers and loss of transverse striations. Occasional areas showed aggregations of lymphocytes. The pituitary was not remarkable.

CASE V. A twenty-two-year-old female with marked weakness of the arms and legs, with atrophy of the muscles of the shoulder girdle, had classical signs and symptoms of thyrotoxicosis. Three weeks after thiobarbital therapy was instituted a four-fold increase in muscular strength had occurred. (Chart 4.)

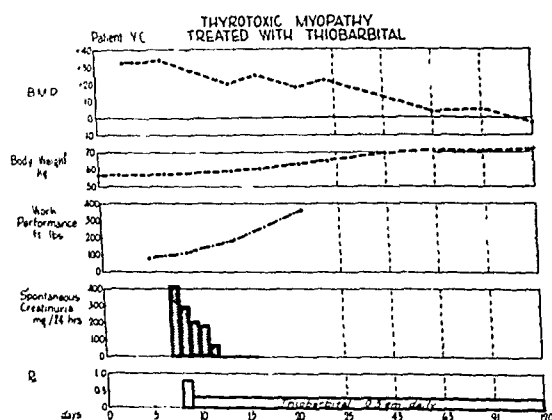


CHART 4.

Y. C., No. M66567, a twenty-two-year-old single housekeeper, entered the Peter Bent Brigham Hospital on June 13, 1944, because of nervousness, weight loss and weakness. She had been in good health until eight months before admission when she had had a severe sore throat and tonsillitis. Following this episode she had felt weak, sweat profusely and lost 10 pounds during the following month. Exophthalmos had then been noted for the first time.

Her most prominent symptom had been the marked weakness of her arms and legs. This progressed so that it had become impossible for her to climb stairs, and she had been unable to raise her arms to comb her hair. Six months prior to admission she had been started on iodine, and there had been a temporary remission in all her symptoms. Two and one-half months before entering the hospital she had stopped the iodine medication. Since then she had lost 30 pounds and had become increasingly

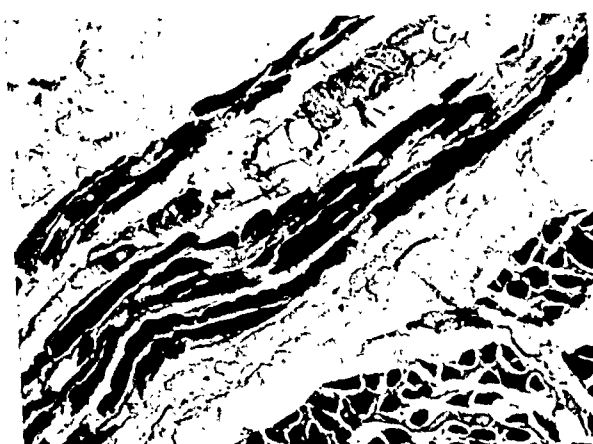


FIG. 3. Patient J. B., skeletal muscle; atrophic muscle bundles with fibrous replacement of muscle fibers. H and E $\times 225$.

more nervous. Sweating had been more marked, and she had noted intolerance to warm weather. There had been considerable muscle weakness especially of the arms and legs with a definite decrease in the size of the muscles. She had had considerable exertional dyspnea and frequent palpitation. Her menstrual periods had always

been regular until two months before admission. At that time she had had an additional period after a seven-day interval.

The patient's past history and family history were non-contributory.

Physical examination on admission showed a well developed and moderately well nourished young woman lying quietly in bed. Her temperature was 98.2°F., pulse 95, respirations 20, blood pressure 140/90 mm. Hg. The skin was warm and moist but of normal texture. There was bilateral exophthalmos, more on the right, with a definite stare, lid lag and convergence defect. Her throat was normal and there was no tremor of the tongue. Her thyroid was considerably enlarged, more so on the right, and there was a definite bruit. Lungs were normal; the heart was not enlarged and sounds were hyperactive. There was a grade III systolic murmur at the left sternal border. No diastolic murmurs were present. The liver edge was just palpable at the costal margin.

There was marked atrophy of the muscles of the shoulder girdle and upper arm, especially the triceps, with marked weakness of the arm especially in extension. There was a fine tremor of the outstretched hands.

Laboratory examination revealed the following: Blood serology was normal. Urine specific gravity was 1.016 with no protein or sugar; spun sediment was clear. Hemoglobin was 14.8 Gm. per cent, hematocrit 38 per cent, and sedimentation rate 14 mm. per hour. White blood count was 6,700 with 70 per cent neutrophils and 23 per cent lymphocytes. Blood urea nitrogen was 5 mg. per cent, total protein 6.5 Gm. per cent, and fasting blood sugar 105 mg. per cent. Stools were negative for occult blood. Venous pressure (method of Burwell) was 115 mm. of water, circulation time (arm to tongue with decholin) was 14 seconds. Urinary 17-ketosteroid excretion was 9.4 mg. per twenty-four hours. On a creatine-free diet her twenty-four-hour urine creatine was 0.42 Gm. Basal metabolic rates before treatment were +33 per cent, +33 per cent and +34 per cent. A chest film showed the heart to be 5 per cent enlarged; there was no substernal thyroid. The work test used consisted in raising a one-pound weight which hung from a rope attached

to a pulley at the foot of the bed. Performance was recorded as the number of times patient could raise the weight by flexing her arm at the elbow. After 1 mg. of prostigmine there was no increase in work performance.

On her 7th hospital day the patient was given a large initial dose of thiobarbital 1.0 Gm. and received 0.3 Gm. daily thereafter. (Chart 4.) There was an immediate and striking reduction in spontaneous creatinuria associated with extremely low creatinine excretion on the day following 1.0 gm. of thiobarbital. (Table III.) It seems probable that this was the result of greatly depleted creatine reserve associated with a rapid retention of creatine in a patient maintained on creatine-free diet. Creatinine values subsequently rose as creatine disappeared from the urine. After one week she improved steadily. Her skin became drier. Her basal metabolic rate dropped to between +18 per cent and +22 per cent at discharge. She gained 7.2 kg. in weight. Before treatment her work performance was 60 with the right arm and 100 with the left. She gradually improved in strength so that by discharge she was able to do 330 on the right and 400 on the left.

The patient was discharged on 0.3 Gm. of thiobarbital daily and was seen in the clinic two weeks later. During that period she gained 4.4 kg. Her gland was smaller, and there was no bruit. Six weeks later her basal metabolic rate was +5 per cent. She had gained 2.0 kg. and was feeling well and strong. She was last seen on November 14, 1944. At that time she was taking 0.1 Gm. of thiobarbital daily, and her basal metabolic rate was -3 per cent. Her weight was well maintained. She felt stronger than she had before the onset of her symptoms and was working in a mill doing moderately hard work. She had no tremor of her hands. Her heart was not hyperactive and no murmurs could be heard. Her muscles were of normal size and strength.

ANALYSIS OF CASES

Age and Sex. The cases which we present and those reported by McEachern and Ross¹¹ are too few to provide reliable statistics on the age and sex incidence of

chronic thyrotoxic myopathy. It is our impression from the data at hand that it occurs in an older age group than does uncomplicated thyrotoxicosis. It also appears that males are frequently affected with a sex ratio different from that reported by Means¹ for uncomplicated thyrotoxicosis in Boston, in which the proportion of males to females is one to four.

Signs and Symptoms. The duration of symptoms in the five patients constituting this report was two to eight months prior to hospitalization. There is no doubt, however, but that symptoms had been present in mild form for a somewhat longer period. In all five patients the presenting complaint was weakness and fatigability. In three, weakness had progressed to such a point that the patients were bedridden and two patients (E. M. and J. B.) were so weak that they were unable to feed themselves.

Weakness of the legs was especially marked. All patients complained of great difficulty in climbing stairs. The most striking muscular atrophy, however, involved the muscles of the shoulder girdle, and in one patient there was winging of the scapula. Involvement of the small muscles of the hands and feet previously noted in patients with chronic thyrotoxic myopathy¹¹⁻¹⁴ did not occur in these patients although it has been observed in a subsequent case. In none of our patients did we observe the fibrillary twitchings which had been seen in several of the patients described by McEachern and Ross,¹¹ nor did we note the facial atrophy described by Ayer, Means and Lerman.¹² One patient (E. M.) presented symptoms of bulbar involvement with thick speech and regurgitation of fluids through her nose.

In all the patients one or more of the signs of thyrotoxicosis were present. In one these were minimal, consisting only of tachycardia and a dry, warm skin. Two had moderate enlargement of the thyroid,

while in two others this was marked. Three of the patients had classical eye signs. These included stare and lid lag in two and definite exophthalmos in a third. In four of the five patients it was possible to make a presumptive diagnosis of thyrotoxicosis by a careful history and physical examination.

Laboratory Data. We observed no clinical improvement in any of our patients after injection of 1.5 mg. of prostigmine. No myograms were made, however. The absence of prostigmine effect is at variance with earlier observations.^{11,15}

In all of our patients there was a significant spontaneous creatinuria ranging from 100 to 590 mg. per twenty-four hours. In all but one patient (G. M.) there was a significant decrease in creatinuria shortly after treatment was instituted. Creatine tolerance tests¹⁶ were done on two patients (G. M. and M. S.), and it was found that there was considerably less creatine retention than normal.

Twenty-four hour urinary 17-ketosteroids¹⁷ were studied in four cases. The two male patients with gonadal atrophy (G. M. and M. S.) had excretions of 8.3 and 8.6 mg. per twenty-four hours respectively, which is a low value when compared to the normal of 12 to 20 mg. for this method. One female patient (E. M.) excreted only 2.7 mg. of 17-ketosteroids per twenty-four hours which is a very low value, whereas another female patient (Y. C.) excreted 9.4 mg. which is normal (9 to 15 mg.). Urinary 17-ketosteroid determinations were not done on patient J. B.

One patient had paroxysmal auricular fibrillation (E. M.), and two had some degree of cardiac enlargement by x-ray (E. M. and Y. C.). Two patients (G. M. and E. M.) showed an abnormally rapid circulation time which decreased to normal after treatment.

Clinical Course. One patient (M. S.) was treated surgically after preparation with

iodine and made a good recovery. Six months postoperatively he showed signs of myxedema which were relieved with thyroid U.S.P. 60 mg.

Two patients (G. M. and E. M.) were treated with thiouracil and one (Y. C.) with a related compound, thiobarbital. The response to treatment was dramatic in all instances. All three patients had a reduction in basal metabolic rate and an increase in strength within two weeks after starting treatment. It is interesting to note that marked objective increase in muscular strength occurred before there was an appreciable gain in body weight. One patient (E. M.) who had been bedridden and unable to feed herself was able to be up and around the ward after one week of treatment with thiouracil.

All four of the patients were completely rehabilitated after treatment of the underlying thyrotoxicosis and were able to take up their occupations which they had dropped at the onset of their symptoms.

The two male patients, despite the fact that they were able to resume their work, felt some residual weakness although there was no visible evidence of muscular atrophy. Because of the gonadal atrophy and low urinary 17-ketosteroid excretion, these patients were given 30 mg. daily of methyl testosterone. On this regimen both noted an increase in muscular strength. In one patient injections of testosterone propionate were substituted with the same result as with methyl testosterone orally. At the time of the testosterone treatment neither of these patients was thyrotoxic.¹⁸

Pathology. One patient (J. B.) with marked atrophy and with little clinical evidence of thyrotoxicosis was admitted to the hospital in a moribund state and died before response to treatment. Pathological examination showed important changes in the thyroid, adrenal, and skeletal muscles. The thyroid (Fig. 1) showed the typical

picture of hyperplasia with large irregular cells and absence of colloid in the acini. The adrenal (Fig. 2) showed atrophy of the zona glomerulosa. The skeletal muscle (Fig. 3) showed many of the changes described by Askanazy.¹⁹ There was marked atrophy with fatty infiltration of the muscles, loss of transverse striations, and replacement of muscle fibers by fibrous connective tissue. In some areas infiltration of lymphocytes was present.

The thyroid removed at operation in patient M. S. showed hyperplasia with iodine involution. It weighed 38.5 Gm. Some of the acini were small, devoid of colloid and lined with high columnar epithelium. Others were larger, filled with colloid and lined by flattened epithelium.

MYASTHENIA GRAVIS AND THYROTOXICOSIS

The combination of myasthenia gravis and Graves' disease is rare. To date six cases have been reported.²⁰⁻²⁵ This association is of considerable interest, since the myasthenia of chronic thyrotoxic myopathy superficially resembles myasthenia gravis and may easily be confused with it. Secondly, it is important to detect thyrotoxicosis when it occurs in the presence of true myasthenia gravis, since the correction of the underlying thyroid disorder may markedly improve the course of the disease.

Case Reports and Observations. We wish to present another instance of the combined diseases (myasthenia gravis and thyrotoxicosis) and also to present a follow-up on a second case previously described.²⁵ Data on the clinical courses of the two patients have been summarized in Table II.

CASE VI. A female, aged fifty-nine, had blurred vision, difficulty in accommodation, ptosis of the eyelids and minimal signs of thyrotoxicosis. Treatment with thiobarbital in the absence of prostigmine was followed by a reduction in basal metabolic rate and increase in

Chronic Thyrotoxic Myopathy—Thorn, Eder

TABLE II
MYASTHENIA GRAVIS AND THYROTOXICOSIS

Patient.....	J. C. Case vi	N. G. Case vii
Sex and age.....	Female, 59 years	Female, 50 years
Duration of symptoms	Eye changes 6 years; 1 month generalized weakness	9 years myasthenia gravis
Thyroid enlargement.	0	+
Eye signs.....	Ptosis	Ptosis, exophthalmos, ophthalmoplegia
Tremor.....	0	+
Muscular involvement	Generalized weakness of all muscles; ptosis and diplopia; regurgitation of fluids	Marked generalized weakness, ptosis, diplopia
Fasciculation.....	0	0
Initial basal metabolic rate—%.....	+17	+46
Spontaneous creatinuria mg./24 hours	220	420
Creatine tolerance test*		
% retention of ingested creatine	60	22
Cardiac enlargement.	0	+
Prostigmine test.....	Marked improvement	Marked improvement
Treatment.....	Iodine followed by thiobarbital and prostigmine	Iodine followed by subtotal thyroidectomy
Result.....	Definite increase in muscular strength; ptosis disappeared	Four-fold increase of strength and gradual reduction of prostigmine requirement
Basal metabolic rate after treatment—%	—6 (5 months)	+3 (6 years)

* Normal for males 85–100% retention; normal for females 80–95% retention.

TABLE III
URINARY CREATINE AND CREATININE FOLLOWING THE ADMINISTRATION OF THIOBARBITAL
Patient: Y. C.

Date	Dose of Thiobarbital Gm.	Urinary Creatinine Gm.	Urinary Creatine Gm.
6/18–19	0	0.7	0.4
19–20	1.0	0.7	0.3
20–21	0.3	0.5	0.2
21–22	0.3	0.8	0.2
22–23	0.3	0.8	0.1
23–24	0.3	1.1	0.0
24–25	0.3	0.9	0.0
25–26	0.3	0.5	0.0
26–27	0.3	0.7	0.0
27–28	0.3	0.7	0.0

Patient maintained on a low creatine diet (meat free) throughout this study.

muscular strength. Treatment with prostigmine alone prior to above therapy also resulted in improvement. (Chart 5.)

J. C., No. M66069, an Italian housewife, aged fifty-nine, entered the Peter Bent Brigham

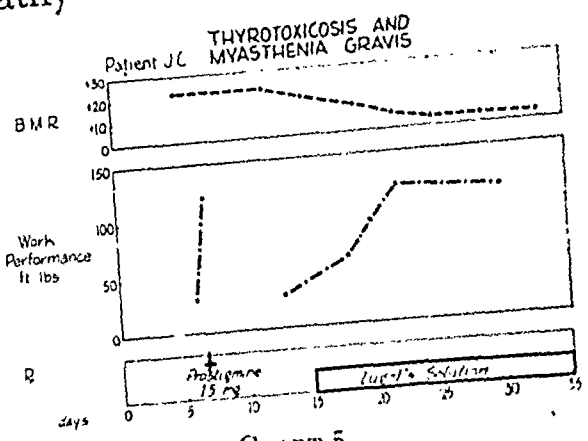


CHART 5.

Hospital on March 20, 1944, complaining of intermittent muscular weakness and pain of two years' duration. She had been well until seven years before admission when she had noted weakness of her left leg on walking. One year later she had begun to have blurred vision with difficulty in accommodating, ptosis of her eyelids and imbalance of her ocular muscles with difficulty in moving her eyes and with diplopia. She had been given prostigmine by her local physician with complete relief of symptoms at first. She had taken the medication sporadically and had been moderately well until three years before admission when she had developed "tolerance" to the drug. Ptosis had continued as a predominant symptom with little oculomotor difficulty. She had had marked weakness and easy fatigability. One month before admission there had been a marked exacerbation of her symptoms. She had developed extreme ptosis. Her legs had become so weak that she had not been able to climb stairs, and finally she had to go to bed. Two weeks before admission she had had difficulty in swallowing for the first time.

There was no past history of intolerance to warm weather, sweating, nervousness or tremor. Family history was non-contributory. Physical examination on admission showed a well nourished, middle-aged woman lying in bed. Movement was difficult and occasioned considerable pain in her muscles. Her temperature was 99°F., pulse 120, respirations 28, blood pressure 160/100 mm. Hg. She spoke clearly. There was no significant lymphadenopathy. There were marked hypertrophic changes in the terminal phalanges of the fingers. Both eyelids showed marked ptosis, more on the left. Extra-ocular movements were weak and un-



FIG. 4. Patient J. C. prior to treatment.



FIG. 5. Patient J. C. twenty-five minutes after administration of 1.5 mg. of prostigmine subcutaneously.

coordinated with inability to look upward with both eyes and weakness of lateral movement on the left. Pupils reacted normally. Fundi appeared normal and the throat was also normal. There was no apparent difficulty in swallowing. Her thyroid was not enlarged, lungs were normal, the heart was not enlarged, sounds were not hyperactive and rhythm was regular and rapid. There was a grade 1 systolic murmur at the base. The abdomen was normal.

There was weakness of all muscle groups but no atrophy. There were no fibrillary twitches or tremor. Reflexes were hypoactive but equal on both sides.

Laboratory examination revealed the following: Blood serology showed nothing abnormal. Urine showed a specific gravity of 1.012 with no protein and a trace of sugar on admission. Spun sediment contained no red cells, 0-3 white cells, and no casts. Hemoglobin was 14 Gm. per cent, hematocrit 42 per cent, white cell count 5,700 with 69 per cent neutrophils, blood urea nitrogen was 15 mg. per cent, total protein 5.9 Gm., fasting blood sugar 107 mg. per cent, cholesterol 272 mg. per cent, calcium 5.0 m.Eq. per liter, and phosphorus 1.9 m.Eq. per liter.

The stool was normal. Initial basal metabolic rates were +17 per cent and +12 per cent. She excreted 0.59 Gm. of creatinine and 0.22 Gm. of creatine per twenty-four hours. Creatine tolerance test showed retention of 85 per cent of the test dose. X-ray film of the chest showed some coarsening of the lung markings. The heart was transverse in position but not enlarged. Films of the skull showed mild hyperostosis frontalis interna. An electrocardiogram was normal except for the presence of Q_3 . The intravenous glucose tolerance test showed a rise to 365 mg. per cent with a return to normal in two and one-half hours.

Diagnosis of myasthenia gravis (Chart 5) was definitely established by striking improvement with prostigmine therapy and by the marked exacerbation of signs and symptoms after quinine therapy. (Figs. 4, 5 and 6.) Because of persistent tachycardia, warm, moist skin, slight elevation of the basal metabolic rate and the spontaneous creatinuria, thyrotoxicosis was suspected. She was given iodine with a resultant drop in basal metabolic rate from +22 per cent, +22 per cent, and +17 per cent before treatment to +12 per cent in five days, +7 per

cent in eight days and thereafter +4 per cent. Basal pulses dropped from between 80–90 to 70–80. Her muscle strength (without prostigmine) improved considerably; before starting the iodine therapy she was able to raise a 6-pound weight only ten times; nine days after taking iodine she was able to raise it twenty times. Spontaneous creatinuria dropped to 0.10–0.04 Gm. per twenty-four hours sixteen days after starting the iodine. These facts plus the marked improvement in well-being indicated hyperthyroidism. Consequently she was started on thiobarbital 0.1 Gm. daily. In addition she was given prostigmine which caused a more marked increase in muscular strength. She was discharged on 120 mg. of prostigmine bromide by mouth and thiobarbital 0.1 Gm.

When seen one month later she was definitely improved. She was less weak and was able to climb stairs and to comb her hair, which she could not do before coming to the hospital. She had no ptosis or diplopia. Basal metabolic rate was +9 per cent.

Five months later she did not appear to be doing well; her appetite was poor and she had lost 15 pounds. On 150 mg. of prostigmine daily she had no ptosis but could climb stairs only with difficulty. She complained of being cold most of the time, and her skin was dry and cool. Basal metabolic rate was –6 per cent. Prostigmine was raised to 180 mg. daily, and thiobarbital was stopped.

The patient was last seen August, 1945. At that time she was considerably stronger and able to get around without difficulty, and she had reduced her daily intake of prostigmine to 90 mg. from the earlier requirement of 180 mg. daily. The thyroid gland was firm and twice normal size. There was no evidence of thyrotoxicosis, her basal metabolic rate being –8 per cent.

CASE VII. A female, fifty years of age, received prostigmine therapy for myasthenia gravis over a period of nine years with considerable benefit. During this period thyrotoxicosis was suspected but never proved. Following the administration of iodine, there was a reduction in basal metabolic rate and creatinuria. Following subtotal thyroidectomy a striking improvement in muscular strength occurred, and a great decrease in prostigmine requirement was noted.



FIG. 6. Patient J. C. following the administration of quinine sulfate (1.2 Gm. total dose) given over a period of ten hours.

N. G.,* No. M145931, a negro school teacher, fifty years of age, was first seen at the Johns Hopkins Hospital on February 5, 1929, complaining of double vision and drooping of the eyelids for the previous three months.

Physical examination showed a poorly nourished colored woman with tachycardia and moist skin. There was marked ptosis of both eyelids, left external strabismus and bilateral exophthalmos. The thyroid was not enlarged, but an audible bruit was present. The heart was enlarged, and there was an apical presystolic rumble. Skeletal muscles contracted strongly at first but fatigued easily. Blood, urine and spinal fluid were normal. Basal metabolic rate ranged between +10 per cent and +36 per cent. During subsequent admissions she complained of increasing weakness of the extremities and trunk with difficult breathing. In November, 1930, she received x-ray treatment over the thyroid gland with some improvement in strength. In September, 1937, she was started on prostigmine, and there was considerable improvement. Treatment could not be continued, however,

* This case was previously reported by Thorn and Tierney.²⁵

because of diarrhea and increased menstrual flow. In July, 1938, she was seen again because of an exacerbation of her symptoms. At this time she had a five-week history of increased nervousness, tremor of her hands, sweating, palpitation and weight loss despite increased appetite. She had marked weakness of her arms and legs so that she was unable to walk without assistance. Physical examination showed, in addition to the findings previously noted, increased nervousness, exophthalmos, bilateral ptosis and ophthalmoplegia. The thyroid was enlarged. There was marked weakness of her skeletal muscles and a coarse tremor. Her basal metabolic rate was +46 per cent. Serum cholesterol was 192 mg. On a creatine-free diet the spontaneous urinary creatine excretion was .420 Gm. per day. In the creatine tolerance test she retained 22 per cent of the test dose. After these preliminary studies she was given Lugol's solution. Her creatine excretion fell to .050 Gm. per day, and 59 per cent of the oral dose of 2.61 Gm. of creatine was retained as compared to 22 per cent before iodine therapy. Her basal metabolic rate decreased slightly during this period. After twenty-five days of iodine treatment a subtotal thyroidectomy was performed. Postoperatively there was general improvement in strength, and she was soon able to walk even in the absence of prostigmine therapy, but the ptosis and ophthalmoplegia did not change appreciably. With prostigmine treatment after operation the ptosis disappeared completely, and she had sufficient strength to return to work.

In the six and one-half years since operation her prostigmine requirement has steadily dropped so that at the present time she takes less than 15 mg. per day to maintain her strength. During this period she has been able to continue her work as a school teacher, although there is still residual weakness of her face and skeletal muscles on sustained effort.

Analysis of Cases. The two patients (J. C. and N. G.) with myasthenia gravis who developed thyrotoxicosis were females, aged fifty-nine and fifty years, respectively. One had had symptoms of myasthenia gravis for six years and symptoms of hyperthyroid-

ism for one month. The other had been followed for nine years before a diagnosis of thyrotoxicosis was definitely established. Both were typical cases of myasthenia gravis with ptosis, oculomotor weakness and moderate generalized weakness. Both responded to prostigmine. In one patient signs of thyrotoxicosis were minimal and consisted only of slight thyroid enlargement, tachycardia and warm moist skin. The other patient had an enlarged gland, with exophthalmos and tremor of hands. Neither patient showed striking muscular atrophy, and weakness was of the myasthenia gravis type, i.e., it became more marked on sustained effort. There were no fibrillary twitchings. Both patients had elevated basal metabolic rates of +17 and +46 per cent, respectively. Both had spontaneous creatinuria of 220 and 420 mg. per twenty-four hours, respectively. Both showed abnormally high creatine excretions following the administration of creatine. On test doses of iodine there was a definite increase in strength of muscles, and there was a drop in the spontaneous creatinuria which does not occur in uncomplicated myasthenia gravis treated with iodine.²⁵ One patient was treated with thiobarbital and the other had a subtotal thyroidectomy performed. In both there was a gradual increase in muscular strength. The prostigmine requirement in the one patient followed for six and one-half years gradually declined so that at the end of that period she was taking occasional doses of 15 mg. per day.

COMMENTS

In these patients with striking myopathic changes in thyrotoxicosis it is of interest to speculate on what particular factors or mechanisms conditioned the response of these individuals in such a way that the myopathic changes predominated in the manifestations of thyrotoxicosis.

Chronic Thyrotoxic Myopathy—*Thorn, Eder*

In our two patients with myasthenia gravis the primary disease was markedly aggravated by thyrotoxicosis. This has also been reported in periodic paralysis.⁶ It has been suggested that an occult primary myopathy underlies many cases of thyrotoxic myopathy. If this were the case, one might expect some evidence of the primary neuromuscular disease to persist following correction of the complicating thyrotoxicosis, but this has not been observed in our five patients.

There is some evidence that an associated disturbance of steroid hormone production occurs in these patients, as indicated by (1) low urinary excretion of 17-ketosteroids in several patients, (2) testicular atrophy in the two males, and (3) the degenerative changes in the adrenal demonstrated in patient J. B. It has been found experimentally that normal rats, when injected with 1 mg. of thyroxin daily for fifteen days, exhibit striking increase in adrenal and testicular weight despite generalized weight loss and wasting.²⁶ This suggests that the steroid hormone requirement may be increased in thyrotoxicosis. That a deficiency of these hormones conditions an over-all unfavorable response in thyrotoxicosis is suggested by the following:

1. Adrenalectomized and/or castrate animals treated with thyroxin have a much higher mortality rate than normal animals treated with the same dose of thyroxin.²⁶

2. Administration of adrenal cortical and gonadal hormones increases the survival rate of normal adrenalectomized and castrate animals given thyroxin.²⁶

3. It is well known clinically that patients with adrenal insufficiency, both primary and secondary, tolerate thyroid administration very poorly.^{1,27}

These factors most certainly have a marked direct effect on muscle. Hertz et al.²⁸ have shown clearly that testosterone propionate has a marked nitrogen retaining

effect even in the presence of thyrotoxicosis. That adrenal cortical hormone has a direct effect on the metabolism of muscle tissue has been clearly shown in the hexokinase studies of Cori et al.²⁹ The hypothesis that the combination of thyrotoxicosis and steroid hormone deficiency can cause marked myopathy certainly appears reasonable.

Creatinuria and a decrease in the creatine and phosphocreatine content of the muscle are common findings in thyrotoxicosis.³⁰ The fact that phosphocreatine is an intermediate in the cycle of energy release in the muscle strongly suggests that the clue to the mechanism of thyrotoxic myopathy may be found in careful study of creatine metabolism in these patients. Many of the steps in the synthesis and utilization of creatine have been elucidated in recent years by a combination of experiments on intact animals and tissue slices and with isotopes of nitrogen and hydrogen. Glycocyamine, the unmethylated creatine, is formed in the kidney by the transfer of the amidine group from arginine to glycine. (Fig. 7.)³¹ This synthesis can be increased by feeding glycine or arginine.³² The glycocyamine formed is methylated in the liver by transfer of a methyl group from the methyl pool (chiefly choline) by way of methionine. (Fig. 8.)³³ In the muscle the creatine is phosphorylated to phosphocreatine (Fig. 9)²⁴ which in turn replenishes the phosphate groups of adenylyl phosphate to form adenosine triphosphate, the breakdown of which has the closest known energy linkage with the actual shortening process of the muscle fiber. In this step creatine phosphate appears to form creatinine, which is eliminated from the body in the urine at the rate of about 2 per cent of the total body creatine per day.³¹

In thyrotoxicosis there are three possible mechanisms for the creatinuria:

- (1) *Increased Synthesis of Creatine in the Body.* In two patients with uncomplicated thyro-

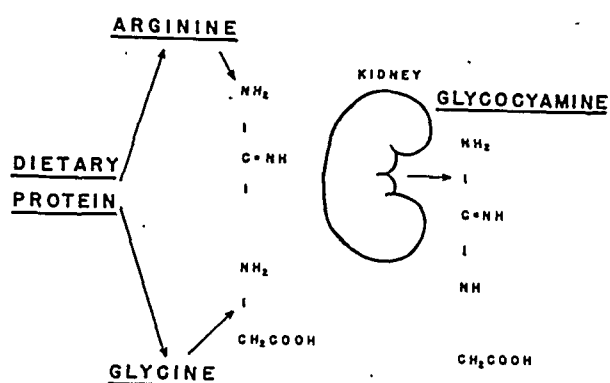


FIG. 7.

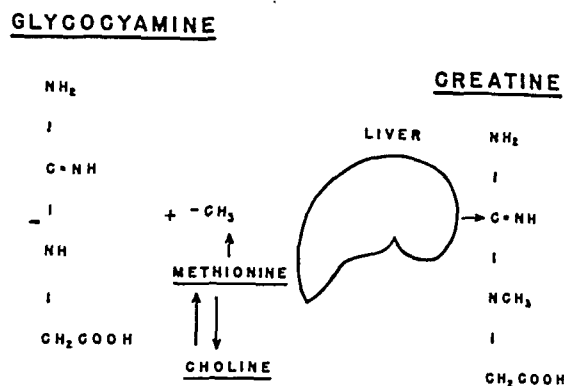


FIG. 8.

toxicosis twenty-four-hour glycocyamine excretion was measured and this was not increased. Although methylation can proceed at a rapid rate, it has been shown that where there is increased synthesis of creatine, as in treatment with methyl testosterone, there is increased glycocyamine excretion.³⁵

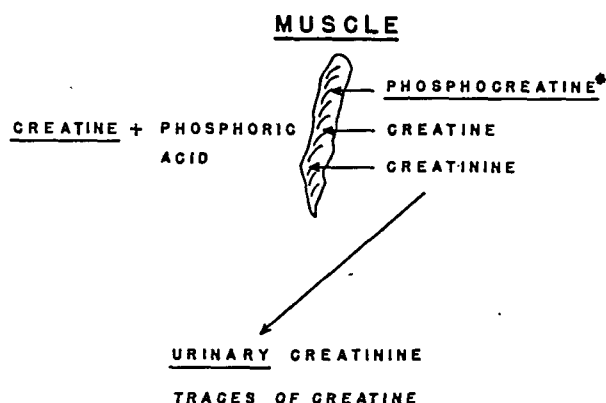


FIG. 9.

(2) *Direct Loss of Creatine from the Muscle.* There is no doubt that this is an important source of urinary creatine. In a rat given thyroxin at the rate of 2 mg. per day the loss of creatine in the urine divided by the weight loss showed a creatine concentration of the order of magnitude of muscle.²⁶ In chronic thyrotoxicosis, however, the muscle stores of creatine alone are probably not sufficient to account for the prolonged creatinuria.

(3) *Failure of Storage and Utilization of Creatine in the Muscle.* That this is a factor in operation in thyrotoxicosis is clearly demonstrated by the decreased creatine tolerance test and by the clinical studies of

Wilkins and Fleischmann.³⁶ A high percentage of a dose of creatine which can be stored easily by a normal person is excreted in the urine of most patients with thyrotoxicosis.³⁷ Since it appears that creatinine is formed from phosphocreatine, the decreased creatinuria so often associated with creatinuria suggests that this failure in storage may result from a failure of phosphocreatine synthesis. In short, the creatinuria of thyrotoxicosis may represent a combination of increased muscle breakdown which is non-specific and parallels the negative nitrogen balance, and a specific failure in creatine utilization and storage.

There appears to be little correlation between the severity of the myopathy and the extent of creatinuria. (Table 1.) In the four patients studied the spontaneous urinary creatine ranged between 100 and 590 mg. per day. There did appear to be a much greater spontaneous creatinuria in the two female patients than in the two male patients. (Table 1.)

It does not appear that chronic thyrotoxic myopathy can be explained on the basis of a simple exaggeration of the usual creatine metabolic defect in thyrotoxicosis, since there is no striking increase in creatine excretion in these patients over that seen in uncomplicated thyrotoxicosis. It is suggested that the defect may be one rather in the direction of failure to maintain adequate synthesis to meet the abnormal demands. This point requires further investigation.

The authors are indebted to Dr. Edwin B. Astwood for the thiouracil and thiobarbital used in these studies, to Dr. Thomas D. Kinney, Department of Pathology, Peter Bent Brigham Hospital, for the pathological studies and the photomicrographs, to Dr. John A. Luetscher, Jr., Johns Hopkins Medical School and Hospital, for the follow-up report on patient N. G., and to Miss Janet E. Clark, Metabolism Nurse, and Miss Marion J. Brian, Research Dietitian, for their valued assistance.

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Disturbance in Salt and Water Metabolism in Hypertension*

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EVIDENCE that the adrenal cortex may be concerned in the development or maintenance of essential hypertension in man has previously been reported.^{1,2} It is of interest that drastic reduction in sodium intake may result in a decline in blood pressure in hypertensive patients,³ possibly through the established influence of the adrenal cortex on salt and water metabolism.

In the course of clinical studies aimed at extending observations on the rôle of sodium in hypertensive vascular disease, it was noted that patients with hypertension differed from control subjects in their response to sodium restriction. It is the purpose of this study to report these findings.

EXPERIMENTAL

All studies were carried out on the wards of the Presbyterian Hospital. Patients with uncomplicated hypertensive vascular disease were included only if the arterial pressure consistently exceeded 140/90 mm. of mercury and in the absence of cardiac pain or insufficiency, renal or cerebral complications or fever. All patients were free of albuminuria, showed normal phenolsulfonephthalein excretion and urine concentration tests, and in all instances the venous pressure was within normal limits. Control subjects included afebrile convalescent patients and healthy volunteers under hospital observation without evidence of cardiac, renal or endocrine disease and with repeatedly normal blood pressure readings.

Both groups were comparable in sex distribution and included as wide an age span as possible. To eliminate any cyclic changes in fluid balance, experiments on female subjects were carried out one to two weeks after the last menstrual period. Thin and obese patients were included in both series studied. All subjects were weighed daily on the same scales before breakfast and before bowel movement.

Sodium chloride was administered by mouth using weighed salt shakers, additional supplements being given in some instances in the form of enteric-coated tablets. Identical salt-poor daily menus were prepared. Repeated direct analyses of aliquots taken from an entire day's cooked diet gave values of between 0.25 to 0.35 Gm. of sodium or considerably less than 1 Gm. of sodium chloride per day. It was found that such diets were not difficult to prepare, permitting the inclusion of sweet butter, salt-free bread, two daily servings of meat and small portions of cream, as well as sugar, fruits and vegetables. These salt-poor diets yielded 1,700 to 2,200 calories and 70 to 80 Gm. of protein, and did not include special ingredients such as dialyzed milk.

Under different conditions of activity and environmental temperature, and with different amounts (4 to 10 Gm.) of added sodium chloride, twelve control and twelve hypertensive subjects were placed on constant food and fluid intake. Paired observations, using one control and one patient

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Hypertension—Perera, Blood

TABLE I
RESULTS OF SODIUM RESTRICTION IN CONTROLS AND HYPERTENSIVES

TABLE I
RESULTS OF SODIUM RESTRICTION IN CONTROLS AND HYPERTENSIVES

					Before and after 24 hrs. Sodium Restriction																	
Normal Subjects	No.	Age	Sex	Ambulation before and during Study	Antecedent NaCl Intake	Weight					Hematocrit Change	Total Serum Protein Change	CO ₂ Content	Serum Chlorides As NaCl	Urine Volume Change	Urine Chlorides						
						Day																
						1	2	3*	4	5												
						(Kilos)																
					Gm.						Kilos	% Cells	Gms./100 cc.	(Milliequiv./Liter)	cc.	Meq./24 Hr. as NaCl						
1	48	M	F	quiet ambul.	5	76.38	76.66	76.42	75.38	74.70	-1.04											
2	15	F	M	bed	5	74.70	74.72	74.73	74.10	74.70	-0.63	+1	0	25.5-26.0	102.8-101.2	+370						
3	34	M	F	average amb.	10	73.06	73.10	73.78	71.58	72.86	-1.60	+1	+0.3	103.1-102.2	+650	130-96						
4	23	F	"	"	7	70.14	70.00	70.03	68.84	69.72	-1.19	+1	+0.1	98.9- 96.3	+475	154-96						
5	33	F	"	"	5	57.14	57.04	56.86	55.54	56.63	-1.32			100.7-100.8	+620	123-62						
6	34	M	F	quiet ambul.	6	72.10	72.08	72.00	71.21	72.04	-0.69				+645							
7	55	M	"	"	5	59.69	59.96	60.55	58.70	60.07	-1.85				+960							
8	87	F	F	bed	5	47.43	47.65	47.87	47.32	47.43	-0.55	-1	-0.3	27.7-28.4	96.5- 97.2	+300						
9	51	M	F	quiet ambul.	4	63.00	62.70	62.70	62.75	63.25	-0.55				+250	77-49						
10	48	F	F	average amb.	8	65.63	65.76	65.93	64.92		-1.01	+2	+0.2	27.5-26.6	100.1- 97.5	+500						
11	20	F	F	quiet ambul.	5	49.74	49.24	49.35	48.66	49.31	-0.69				+220							
12	45	F	"	"	5	69.16	69.28	69.51	68.51	68.90	-1.00											
mean = -1.01																						
Hypertensives											Kilos	% Cells	Gms./100 cc.	(Milliequiv./Liter)	cc.	Meq./24 Hr. as NaCl						
1	44	F	F	average amb.	7	62.12	62.42	62.70	62.22	58.56	-0.48	-2	-0.2	24.2-24.4	104.8-105.2	+300						
2	45	M	M	quiet ambul.	7	59.17	58.91	58.85	58.84	58.56	-0.01	+1	+0.1	27.8-27.8	105.6- 99.5	+100						
3	22	M	M	bed	8	50.11	50.10	50.05	50.10		+0.05	+1	+0.1	26.1-27.9	98.0- 95.2	- 75						
4	44	F	F	quiet ambul.	6	68.52	68.48	68.36	68.15		-0.21		+0.1	104.3-103.3	+100	80-38						
5	44	F	"	"	9	65.00	64.75	64.85	64.53	64.40	-0.32			29.3-28.9	103.2-101.3	+400						
6	45	M	F	average amb.	5	60.50	60.66	60.60	60.13	60.34	-0.47	-1	-0.2	28.1-28.4	101.8-100.0	-160						
7	55	F	F	quier ambul.	8	51.77	51.93	51.61	51.43		-0.18	0	+0.2	27.1-27.5	100.7- 99.6	+160						
8	46	M	F	average amb.	7	58.61	58.30	58.36	58.31	58.19	-0.04											
9	46	F	F	bed	5	50.64	50.50	50.24	50.40		+0.14				-275							
10	61	F	F	quiet ambul.	5	50.70	50.95	51.25	50.80		-0.45				+ 75							
11	63	F	F	average amb.	5	62.70	62.76	62.86	62.69	62.80	-0.17				+200	77-45						
12	36	F	F	quiet ambul.	4	58.00	57.85	57.90	57.67	57.75	-0.23	-1	+0.3	26.6-27.3	101.5- 99.5							
mean = -0.198																						

* Start of 24 hr. sodium restriction.

with hypertension, were made whenever possible. After two days on a constant regimen, the added sodium chloride was withdrawn for twenty-four hours (beginning with breakfast on the third day), but without other change in activity, diet or fluid intake. Sodium chloride administration was resumed on the morning of the fourth day.

RESULTS

In association with rigid sodium restriction for twenty-four hours, a conspicuous weight loss occurred in all of the control non-hypertensive group which was not apparent in any of the hypertensive subjects (Table I, Fig. 1.) After one day without

added salt, the mean weight loss of the control group was 1.0 kg. as compared to 0.2 kg. in the patients with hypertension. Calculation of the standard error of the differences proved these values to be statistically significant. No matter whether a control subject lay in bed with little clothing on a cool day (mean temperature 59°F.), or a warmly clothed hypertensive patient exercised vigorously on a hot day (mean temperature 81°F.), all of the control subjects lost more than 0.55 kg., whereas weight loss among the hypertensive series never exceeded 0.48 kg.

In addition, the control group exhibited a diuresis after salt withdrawal, whereas the hypertensives showed much smaller varia-

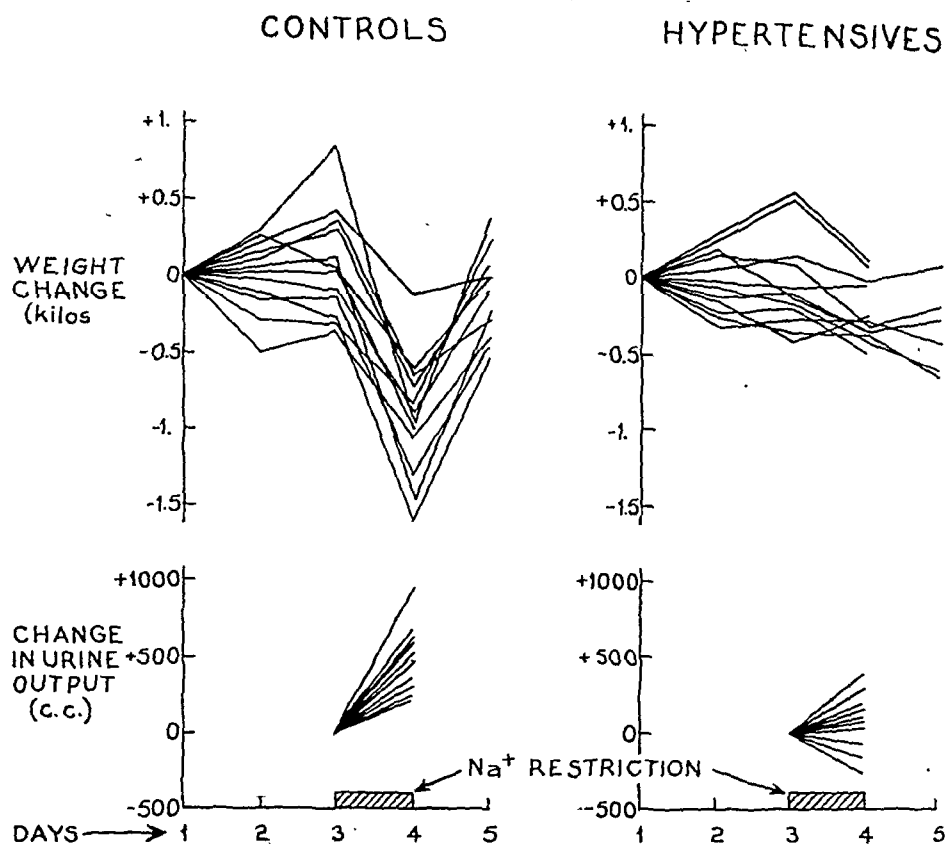


FIG. 1. The effect of salt restriction on weight and urine output in control and hypertensive subjects.

tions in urine output. Furthermore, several in the control group noted increased sweating, insomnia or slight weakness toward the end of the twenty-four-hour period of sodium restriction, none of which symptoms were noted by patients with an elevated blood pressure. Two control subjects, who were later placed on salt restriction for forty-eight hours and developed the above symptoms to a greater extent on the second day, also complained of subjective disturbances similar to those described by McCance in salt-depleted normal individuals.⁴ On the other hand, it was shown repeatedly that hypertensive patients could tolerate weeks of the low sodium diet without discomfort of any kind.

Urine sodium determinations were made on twenty-four-hour samples in two control subjects and in two hypertensives, before and after salt restriction was instituted, on the same day in both pairs, and after identical menus and sodium intake. Following the withdrawal of salt, the sodium values in the

urine decreased to the same extent in both instances.

Urine chlorides usually decreased in control and hypertensive subjects. Significant changes in hematocrit, total proteins, serum CO_2 and chloride determinations were not observed. Blood pressure levels were not materially affected by the twenty-four-hour period of salt withdrawal.

Calculation of sodium and chloride clearances (UV/P) in two control subjects and two hypertensive patients showed little change in the non-hypertensive individuals following salt restriction but a definite reduction in clearance values in the patients with elevated blood pressure.

COMMENTS

It has been shown that non-hypertensive subjects respond differently to the rigid withdrawal of sodium from the diet as compared with a group of patients with uncomplicated hypertensive vascular disease. Regardless of the amount of activity

Hypertension—*Perera, Blood*

or of the antecedent salt consumption, a drastic reduction of sodium intake in control subjects was followed by an immediate and significant loss in weight attributable in part to an associated diuresis. If this was carried much beyond a twenty-four-hour period, a regular pattern of symptoms appeared. Patients with essential hypertension, on the other hand, showed minimal weight change, failed to exhibit a diuresis and were symptom-free.

The decrease in weight in the control group was not entirely explained by the alteration in urine output. As several subjects noted increased perspiration, it is possible that changes in sweat production may have been responsible in part. Preliminary observations suggest that the urine sodium and chloride values were largely influenced by the reduction in sodium and chloride by mouth, rather than by the changes in urine volume, but the net result was a decrease in sodium and chloride clearances in two hypertensive patients studied as compared to minimal change in normal subjects. Whether or not a shift of sodium into cells accompanied the diuresis observed in control subjects remains to be seen.

The mechanism involved in this difference in behavior remains obscure. It is conceivable that the defect is purely renal in origin, secondary to changes produced by hypertension. However, with the exception of the nephrotic syndrome, in which reabsorption is augmented, most kidney disorders involving the tubular elements are associated with a decreased capacity for reabsorption. The effects of a low sodium diet on glomerular filtration and tubular function must be further elucidated.

The inability of hypertensive patients to lose weight and fluids in response to sodium restriction is consistent with the view that the adrenal cortex may be implicated, since the tubular reabsorption of salt and water is

known to be influenced by desoxycorticosterone. Furthermore, it has been repeatedly demonstrated that the arterial blood pressure may rise in normal subjects¹ and may exceed normal limits in a considerable number of patients with Addison's disease in the course of treatment with desoxycorticosterone esters.⁶⁻¹¹ Not only has it been suggested that the abnormal liberation of certain adrenal cortical steroids may be concerned in the etiology of hypertension,² but recent studies have shown that sodium chloride appears essential for pressor and certain other activities of desoxycorticosterone when administered to rats rendered nephritic with nephrotoxic serum.⁵

CONCLUSIONS*

1. Observations have been made on twelve control subjects and twelve patients with uncomplicated hypertensive vascular disease following the rigid withdrawal of sodium chloride for twenty-four hours.
2. Despite an otherwise constant regimen, sodium restriction was followed by significant weight loss and increased urine output in control subjects which was not evident in hypertensive patients, regardless of variations in environmental temperature and physical activity.
3. A disturbance in salt and water metabolism exists in hypertensive vascular disease as judged by the abnormal response to the abrupt and rigid restriction of sodium in the diet.
4. It is suggested that this difference in response may be referable to primary renal changes or, more likely, to changes in the kidney mediated by the adrenal cortex.

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Thiouracil in Angina Pectoris^{*}

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ALTHOUGH the value of total thyroidectomy for severe angina pectoris has been generally recognized, the procedure has fallen into disuse because of the initial risk, subsequent complications and likely myxedema. Accordingly, when the anti-thyroid agent, thiouracil, was introduced, one of the earliest suggestions for its use in other than thyrotoxic states was as a substitute for thyroidectomy in the control of angina pectoris. Here it was expected that a reversible, risk-free chemical thyroidectomy might be performed with results at least comparable to those formerly attained surgically. That this appears to be a valid assumption is attested to by the report of Raab,¹ in which seven of ten patients with angina responded favorably, and that of Ben-Asher,² with eight patients successfully treated.

To determine whether thiouracil is consistently active in this respect, its ability to depress a normally functioning thyroid gland and to lower the basal metabolism must be established. Then, too, toxic reactions from the drug must be infrequent enough not to eliminate too many patients from treatment over an extended period of time. Finally, in this preponderantly subjective disease, a thoroughly objective, skeptical attitude must be adopted by the investigator in evaluating reported changes in the patient's condition.

While there is ample evidence of the thyroid depressant effect of thiouracil in normal animals and in humans with thyrotoxicosis, little data are available demon-

strating a similar action on the normal human thyroid. In the thyrotoxic state positive action becomes manifest in an average six to eight weeks, but in the normal it is reasonable to expect a longer time to elapse if the tightly organized pituitary-thyroid relationship is to be disrupted. Astwood has observed the development of myxedema in normal humans after at least five months' continuous administration of the drug. Similar observations have not been reported by any one else, so that this basic question will be answered only as experience accumulates.

Toxic reactions from thiouracil have an unpredictable incidence of 10 to 15 per cent. These consist mainly of drug fever, skin eruptions, leukopenia and agranulocytosis, and their occurrence appears unrelated to dosage or duration of therapy. However, the risk is not too great if a close watch is kept through repeated blood counts, and the patient is instructed to report promptly any untoward development. Except in the case of the skin reactions or leukopenia, when the drug may be restarted at a lower dosage level without recurrent reaction, drug fever and agranulocytosis eliminate the patient from further treatment.

It is quite obvious that in angina, in which so much of the disturbance is subjective, care must be exercised in evaluating reports of improvement which may be wishfully inspired. Interruption of treatment at intervals, with substitution of placebos, is perhaps the best method of testing the validity

^{*} From the Department of Medicine, Harper Hospital, and Wayne University College of Medicine. Thiouracil and propyl-thiouracil were supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Inc., Pearl River, New York.

of the improvement, though this may invite toxic drug reactions. Oxygen deprivation tests could be carried out periodically but, as between the two methods, the former appears the more practical. Spontaneous improvement must also be thought of in evaluating the results of therapy but there is no way of tagging this factor so that it must stand as a negative quantity in any final summation of results. One final point worth remembering is that the patient with severe angina, for whom a trial of thiouracil may be especially indicated, will not long maintain his enthusiasm for any method of treatment if genuine relief is not obtained.

With these guiding views, studies were made on a group of eight patients with angina, five of whom were observed for a period of approximately one year. In two the disturbance was mild, in two it was moderately severe and in the remaining four severe. On beginning treatment the action of the drug with its possible ill effects was fully explained and the patients instructed to report promptly any ill effects. Basal metabolic rate determinations and blood counts were at first repeated every two weeks and later every four weeks. The initial dose of thiouracil was either 0.4 or 0.6 Gm. daily, divided into two or three equal doses. This was reduced to 0.3 or 0.2 Gm. daily as soon as there was any improvement. Patients were permitted to continue taking nitroglycerin as necessary and were also allowed to use a mild sedative when unable to sleep.

CASE REPORTS

CASE I. S. G., a fifty-two-year old white male, had had attacks of chest tightness and pain radiating down the left arm for almost a year. He was able to continue work as a tailor as long as he took from four to six tablets of nitroglycerin daily. During the month previous to his first visit, however, the attacks of pain became more frequent and severe and were no longer adequately controlled by nitroglycerin.

His activity was greatly limited and he remained closely confined to his home.

His physical examination revealed no distinctive abnormalities. The blood pressure was 150/90, the heart size was normal and there were no murmurs. The EKG showed left axis deviation, small Q_2 , flattened T_2 and inverted T_3 , and the precordial leads were normal. The initial basal metabolism was minus 15 per cent on March 21, 1945.

Thiouracil, .2 Gm. three times daily, was started and the patient advised to continue using nitroglycerin as necessary. Little improvement was noted during the following three months. The basal metabolism readings during this period were minus 11, 6, 18 and 12 per cent. The patient failed to return for further observation.

Comment. In this instance of severe angina, thiouracil administered continuously for three months in a dosage of 0.6 Gm. daily failed to produce any improvement. The lowest basal metabolism level attained was minus 18 per cent.

CASE II. M. A., a fifty-nine-year old white female, developed chest pain and tightness with shortness of breath on exertion ten months previous to her visit in April, 1944. Hypertension had been present for several years. She was somewhat obese, the blood pressure was 168/90 and there was a grade 2 retinopathy. The thyroid showed bilateral nodular enlargement without evidence of toxicity. The heart sounds were forceful but there were no murmurs. She failed to improve during the next ten months in spite of loss of eighteen pounds and the use of aminophyllin and sedation.

In March, 1945, the basal metabolic rate was plus 1 per cent, the blood cholesterol 245 mg. per cent, and the chest x-ray showed no increase in heart size. The EKG showed left axis deviation, small Q_1 and negative T_3 .

Thiouracil, 0.2 Gm. three times daily, was started and continued for six weeks without improvement when the patient failed to return for further treatment. The basal metabolism readings during this interval were plus 3, minus 2 and 0 per cent.

Comment. This patient with mild angina failed to improve after six weeks' continuous administration of thiouracil at the rate of 0.6 Gm. daily. The lowest basal metabolism attained was minus 2 per cent.

CASE III. B. W., a forty-six-year old white male, noted increasing shortness of breath, tightness of the chest with numbness in both arms, and exhaustion following almost any form of exertion during the two years preceding his first visit.

Physical examination was negative, the blood pressure 140/90 and no heart murmurs were heard. X-ray study of the chest showed the heart size at the upper limits of normal. The EKG showed left axis deviation with slurring and notching of QRS and Q_1 , Q_3 , and QCF_3 present.

A regimen of lessened activity, small meals, no tobacco and aminophyllin and sedatives was followed for four months without improvement. In August, 1945, thiouracil, .2 Gm. twice daily, was started, the initial basal metabolic rate being minus 6 per cent. Subsequent determinations at monthly intervals were plus 2, minus 8, 16, 24, 15, 10, 16, 0, 9, 20 and 8 per cent. Improvement was reported at the end of four weeks and the tightness in the chest disappeared after eight weeks. At this point the thiouracil was reduced to .1 Gm. three times daily.

At the end of four months' treatment the basal metabolic rate was minus 24 per cent and the patient's face was puffed, he was sluggish and complained of sensitivity to cold. The blood cholesterol was 324 mg. per cent. The chest tightness and numbness in the arms had returned but this gradually disappeared during the next two weeks on a reduced dose of .1 Gm. thiouracil twice daily. Treatment was continued for another four months, then terminated. The patient had been entirely symptom-free during this latter period as well as during the subsequent four months' interval without medication. No change was found in the EKG or chest x-ray at this time.

Comment. This patient with moderately severe angina, starting with an initial basal metabolism of minus 6 per cent, showed

improvement at the end of eight weeks on 0.4 Gm. thiouracil daily. After four months' treatment the basal metabolic rate dropped to minus 24 per cent and myxedema developed. Symptoms returned at this time but disappeared promptly on a lowered dosage of 0.2 Gm. thiouracil daily which was continued for four months. He has remained symptom-free during the subsequent four months without medication.

CASE IV. M. C., a fifty-two-year old white male, had recovered from an acute anterior myocardial infarction in 1941 which had been preceded by several months of precordial tightness brought on by exertion, emotional disturbance and exposure to cold. He remained symptom-free until January, 1943, when the chest tightness returned. At this time the EKG showed absent R in lead IVF with negative T and the chest x-ray showed no increase in heart size.

The attacks were mild and irregular until December, 1944, when they increased in severity and frequency, requiring six to eight tablets of nitroglycerin daily for control. Then, following a train wreck, pain and tightness were markedly aggravated and even thirty to forty tablets of nitroglycerin daily failed to give sufficient relief to allow him to venture out of the house. Repeated EKG studies failed to show any change from previous tracings.

Early in June, 1945, thiouracil, .2 Gm. three times daily was started. The initial basal metabolic rate was plus 5 per cent. There was considerable gastric distress from the drug during the first two weeks, but no other reaction was noted. Little improvement occurred during the first eight weeks' treatment, the basal metabolism readings in this period being 0, minus 22, 5 and 13 per cent. In another two weeks, however, there was considerable improvement; he was able to go out for short walks and required only two or three tablets of nitroglycerin daily. The basal metabolism was now minus 16 per cent and the thiouracil was reduced to 0.4 Gm. daily.

At the end of five more weeks the patient was quite comfortable although the basal metabolic

rate was minus 3 per cent. Thiouracil was discontinued for one week and there was a prompt return of symptoms and the basal metabolism rose to plus 7 per cent. Medication was resumed and the distress was relieved in three to four days.

During the next ten weeks the patient remained quite comfortable, requiring only an occasional tablet of nitroglycerin following considerable exertion. The basal metabolism readings during this period were plus 6, minus 9 and plus 11 per cent. The thiouracil was discontinued at this point because the patient was leaving the city. After a little over six months' treatment there was considerable improvement and the patient had gained ten pounds.

Shortly after his arrival in California the attacks of distress recurred and his attending physician prescribed 3 gr. aminophyllin with $\frac{1}{4}$ gr. phenobarbital four times daily, with nitroglycerin to be taken as needed. He remained symptom-free on this regimen for four months and has been free of all discomfort without any medication since his return home three months ago.

Comment. This patient with severe angina coming on several years after a healed myocardial infarction showed improvement after ten weeks of thiouracil, 0.6 Gm. daily. The initial basal metabolic rate was plus 5 per cent and a level of minus 16 per cent was noted at the time of improvement. Symptoms recurred when the thiouracil was discontinued, and disappeared shortly after it was restarted. There was marked improvement after six months' therapy and a subsequent recurrence was controlled with aminophyllin and sedation given over a period of four months. The patient has been symptom-free without medication for three months.

CASE V. L. N., a fifty-one year old white female, had fully recovered from an attack of acute myocardial infarction in October, 1943, but developed chest pain and tightness on exertion, after meals and emotional stress in June, 1945. She had had a goiter in 1925, with nervousness

and bulging eyes, which had responded to ten months' medical treatment. In 1937, a lumbar sympathectomy was performed for hypertension.

She was a plethoric, thick-necked individual with prominent eyes but no true exophthalmos. The thyroid was not palpable. The blood pressure was 170/130, there was grade 2 retinopathy, accentuated aortic second sound, and a rough systolic murmur at the left sternal border. The x-ray showed no increase in heart size and the EKG showed left ventricular preponderance. The basal metabolic rate was minus 16, the non-protein nitrogen 33.3 mg. and the cholesterol 210 mg. per cent.

On August 4, 1945, .2 Gm. thiouracil twice daily was started. On August 27th, the basal metabolism was minus 19 per cent and the patient reported no distress or pain. The blood pressure was 140/90. The dosage was reduced to .1 Gm. three times daily and the improvement continued for the next nine weeks with the basal metabolic readings at minus 17, 16, 14, 19, 16 and 12 per cent. The blood pressure ranged between 140 and 148 systolic and 100 to 110 diastolic.

Within another four weeks, as cold weather set in, there was gradual recurrence of pain and distress and the thiouracil was gradually increased to .6 Gm. daily. The basal metabolic readings were minus 8 and minus 11 per cent and the blood pressure had returned to 170/110. After two weeks on the increased dosage, improvement occurred and the basal metabolism dropped to minus 20 per cent while the blood pressure receded to 150/80, then 130/80, and 120/80. In another four weeks the basal metabolism was minus 23 per cent, there was puffiness of the face and eyes and the patient complained of extreme sensitivity to cold. The blood cholesterol was 369 mg. per cent. Thiouracil was reduced to 0.4 Gm. daily and the puffiness gradually receded while the patient remained totally free of discomfort.

Treatment was discontinued after a total of seven months and within a week there was recurrence of all former symptoms. At this time the EKG and the chest x-ray showed no change. Propyl-thiouracil was now started but a dosage of 25 mg. three times daily for three weeks failed to control the disturbance. A greater measure

of relief followed when the dose was increased to 25 mg. five times daily but the control was not as good as that obtained with thiouracil. This level was continued for seven weeks during which the basal metabolic rate was minus 16, 10, 11, 12 and 10 per cent. It was planned to increase the dosage but the sudden death of a brother with angina precipitated a marked increase in pain necessitating hospitalization and oxygen administration for relief. EKG studies failed to reveal evidence of myocardial infarction.

Comment. This patient with severe angina and hypertension, who had formerly recovered from an acute myocardial infarction, showed improvement after three weeks of thiouracil 0.4 Gm. daily. The basal metabolic rate dropped from minus 16 to minus 19 per cent. On reducing the drug to 0.2 Gm. daily, symptoms returned and the basal metabolism rose to minus 8 and minus 11 per cent. When increased to 0.6 Gm. daily, improvement recurred and the basal metabolism dropped to minus 20 per cent, then to minus 23 per cent, when myxedema developed. On a maintenance dose of 0.4 Gm. daily the patient remained symptom-free. After seven months' treatment, thiouracil was stopped and symptoms recurred within a week. Propyl-thiouracil was substituted for ten weeks but the dosage was insufficient for control comparable to that obtained with thiouracil.

CASE VI. O. H., a forty-two-year old white male, had been having attacks of precordial pain and distress for nearly two years. These were most severe upon exertion following a meal, with the pain radiating into the throat and left shoulder and arm. Relief at first followed rest; later nitroglycerin became necessary; more recently the ineffectiveness of both these measures kept the patient from his work.

Examination disclosed an accentuated second aortic sound, a rough systolic murmur at the left sternal border and a blood pressure of 148/90. X-ray study showed no cardiac en-

largement although there was some increase in prominence of the aorta. The EKG showed left axis deviation; Q_1 and Q_2 ; depressed ST_1 with diphasic T_1 ; low voltage; positive T_2 and T_3 and absent R_3 . The precordial leads showed absent RCF_2 with elevated ST and positive T; deep QCF_4 , elevated ST and negative T; QCF_5 with depressed ST and negative T. The basal metabolic rate was plus 6 per cent.

Thiouracil, .2 Gm. three times daily, was started in August, 1945. In six days the patient developed generalized joint pain and headache which continued for four days. No thiouracil was taken for eight days then it was resumed at the lower level of .1 Gm. three times daily. No further reaction occurred.

Four weeks after beginning treatment the patient had returned to part-time work because his attacks of pain were fewer and less severe. The basal metabolism was minus 9 per cent. In another two weeks improvement was still more marked and full-time work was resumed. The basal metabolism was now minus 19 per cent. The drug was reduced to 0.1 Gm. twice daily and continued at this level for the next eight weeks, the basal metabolic readings being minus 9, 16 and 6 per cent. Coincident with the last reading there was reported a return of distress and medication was increased to 0.1 Gm. three times daily.

In the following eighteen weeks the patient was able to continue regularly at his work without notable discomfort. The basal metabolic readings during this interval were minus 13, 11, 19, 22 and 20 per cent. At this point, after eight months' continuous treatment, both lobes of the thyroid became palpable but there were no signs of myxedema. Thiouracil was discontinued but pain recurred within two days and became more marked during the next four days. Propyl-thiouracil, 25 mg. four times daily, was substituted and improvement followed after two days. This treatment was continued for twelve weeks during which there was very little discomfort and the basal metabolism was minus 23, 3 and 9 per cent. Propyl-thiouracil was discontinued and eleven months of anti-thyroid therapy terminated. The patient has continued symptom-free for one month. The EKG showed no change.

Comment. This patient with severe angina developed a drug reaction six days after starting 0.6 Gm. thiouracil daily. After a weeks' abstinence he was able to take 0.3 Gm. daily without difficulty. Improvement was noted first after four weeks and was more pronounced at the end of six weeks with corresponding basal metabolic readings of minus 9 and minus 19 per cent. Bilateral thyroid enlargement was noted after eight months' treatment. Reduction of the drug to 0.2 Gm. daily and its discontinuance allowed pain to recur. Propyl-thiouracil, 100 mg. daily, successfully controlled the disturbance for three months. After eleven months' anti-thyroid treatment the patient has remained free of angina for one month without any medication.

CASE VII. J. K., a sixty-year old white female, had hypertension for two years previous to an attack of acute posterior myocardial infarction in February, 1944. Recovery was uneventful but in September she began having occasional attacks of precordial pain following exertion and relieved by rest. Gradually these attacks became more severe and frequent in spite of continuous administration of aminophyllin and sedatives, and required six to eight tablets of nitroglycerin for their control. They would follow each meal and would come on after walking a short distance. Pain was now referred to the throat and the left shoulder and arm.

Examination showed forceful heart sounds, accentuation of the aortic second sound and a blood pressure of 140/90. The EKG showed left axis deviation with absent R in leads 3 and 4F and elevated ST with diphasic T in this latter lead. The basal metabolism was minus 6 per cent.

In September, 1945, thiouracil 0.1 Gm. three times daily, was started with little improvement during the following month. The basal metabolism was now minus 8 per cent. In another month, however, there was considerable improvement, the attacks being fewer and less severe with the need for nitroglycerin much reduced. The basal metabolism was now minus 16 per cent.

Thiouracil was discontinued at this point but within a week there was a marked increase in pain and discomfort so medication was resumed, with relief following in three to four days. She continued to improve steadily during the following three months and after a total of six months' therapy had very little discomfort and no longer needed nitroglycerin. The basal metabolic readings during this period were minus 12, 16 and 19 per cent.

Propyl-thiouracil, 25 mg. four times daily, was substituted for the thiouracil without change in the patient's condition. During the three months it was given the basal metabolism was minus 20, 19 and 17 per cent. She has been symptom-free for one month on no medication.

Comment. This patient with moderately severe angina developing several months after an attack of myocardial infarction showed improvement after two months of thiouracil, 0.3 Gm. daily. The initial basal metabolism was minus 6 per cent and at the time of improvement it was minus 16 per cent. Symptoms recurred when the thiouracil was discontinued and improved when it was resumed. Marked improvement was attained at the end of six months and this was sustained for another three months with 100 mg. daily of propyl-thiouracil substituted for the thiouracil. The patient has remained well for one month without any medication.

CASE VIII. S. D., a fifty-eight-year old white male, developed attacks of precordial tightness with radiation to the throat upon exertion five years after he had recovered from an acute anterior myocardial infarction. These increased in frequency and nine months after the onset required five to six tablets of nitroglycerin for their control.

On examination the patient was about twenty pounds overweight, the heart sounds were distant with no audible murmurs, and the blood pressure was 100/80. The EKG showed a small Q_1 , negative T_3 , absent R and elevated ST with upright T in CF_2 and CF_4 , and a QCF_5 . The basal metabolism was plus 2 per cent.

On October 9, 1945, thiouracil, .1 Gm. three times daily, was started. There was little change during the first month although the basal metabolic rate had dropped to minus 9 per cent. At the end of another month the patient reported very little distress requiring only an occasional tablet of nitroglycerin. The basal metabolism was now minus 12 per cent. The patient failed to report for further observation.

Comment. In this instance of mild angina coming on several years after an acute myocardial infarction, there was apparent relief after two months of thiouracil, 0.3 Gm. daily. The basal metabolic rate had dropped from plus 2 to minus 12 per cent. However, the period of observation was too brief to permit classification of the result.

SUMMARY

Of eight patients with angina treated with thiouracil, five were improved, two unimproved, and one, though showing some evidence of improvement, had not been observed long enough to permit classification of the result. The two that did not respond were treated for three months and six weeks respectively. One of these, with severe angina, showed a change in the basal metabolic rate from minus 15 to minus 18 per cent. The other, with mild angina, dropped from plus 1 to minus 2 per cent. The patient with the unclassified result had a mild angina, was treated for two months, the metabolism changing from plus 2 to minus 12 per cent.

By contrast, the five who improved were treated for eight, six, seven, eight and six months, respectively, an average of seven months. Little if any improvement became manifest before two months had elapsed. The lowest basal metabolic levels reached in these patients were minus 24, 22, 23, 23 and 20 per cent.

In patients B. W. and L. B. myxedema developed at four months and five months,

respectively. Bilateral thyroid enlargement appeared in patient O. H. at the end of eight months' treatment. This constitutes valid evidence for the ability of thiouracil to suppress the normal thyroid if it is administered consistently over a long enough period of time.

Toxic reactions to the drug offered little interference in the treatment of this small group. Patient M. C. developed gastric distress at the onset which disappeared quite promptly. Patient O. H. developed joint pains and headache on the sixth day, which cleared on stopping medication for one week and did not recur on a lower dosage level.

Propyl-thiouracil, because of its lesser toxicity, was substituted for thiouracil in three patients after improvement had appeared. In patient L. B. three months' administration at 75 to 125 mg. daily failed to hold the gain made with thiouracil. One hundred mg. daily over a three months' period held the ground previously gained by patients O. H. and J. K..

Four of the five improved patients continued symptom-free without further treatment: Patient B. W. for four months, patient M. C., three months, and patients O. H. and J. K. one month each. In accounting for this and the improvement in general, it may well be claimed that a period of time alone, comparable to that devoted to treatment with thiouracil, would be sufficient to permit development of enough collateral circulation to overcome the anoxia and pain. While this might account for the ultimate improvement and freedom from attacks after treatment had been terminated, it would make no allowance for the part played by the thiouracil in lowering the metabolism, reducing the demands on the heart muscle, and in decreasing the latter's sensitivity to adrenalin. This action, though slow in developing, is apparently instrumental in controlling the symptoms in

angina while modification of existing circulatory deficiencies is being accomplished through improvement in the collateral circulation.

CONCLUSION

From the data obtained in the above study it is fair to conclude that thiouracil exerts a suppressive action on the normal

thyroid when given over a long enough period of time, and effects chemical thyroidectomy benefitting the patient with angina pectoris.

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The Effects of Quinacrine (Atabrine) Suppression on the Course of Pacific Vivax Malaria*

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THE studies reported here were designed to determine the effect of quinacrine suppression on the course of recurrent Pacific vivax malaria in a non-endemic area.

MATERIAL

Group A. Forty-nine patients were treated at this hospital for acute attacks of vivax malaria of Pacific origin with 2.8 Gm. quinacrine in seven days and were then placed on a suppressive regimen of 0.1 Gm. quinacrine daily for 150 days. Medication was administered under supervision to insure ingestion of the drug. During the period of suppression, thick malaria smears were examined weekly. Fasting plasma quinacrine levels were determined¹ every two weeks during and for one month after the period of suppression.

Group B. As a control group, sixty-nine patients were treated for acute attacks of Pacific vivax malaria with 2.8 Gm. quinacrine in seven days without subsequent suppressive medication.

Group C. Four hundred four patients who were treated for acute attacks of Pacific vivax malaria provided information on the relationship of the incidence of recurrence to the number of previous attacks. Quinacrine, chloroquine (SN 7618),^{2,3} or quinine in various dosage regimens were used in

treatment of these attacks.* The sixty-nine patients in Group B are included in this analysis. The patients are divided into five groups: (1) 116 patients who had had no previous attacks of malaria; (2) 186 patients with one to five previous attacks; (3) forty-nine patients with six to ten previous attacks; (4) forty patients with eleven to twenty previous attacks; and (5) thirteen patients with twenty-one or more previous attacks. The incidence of recurrence within 120 days in each of these groups was determined.

Following the end of antimalarial medication, whether for suppression or for treatment of an acute attack, all patients (Groups A, B, and C) were observed until the first subsequent relapse, or, if no relapse occurred, for 120 days. During this period of observation, thick malaria smears were examined once or twice weekly. No anti-malarial therapy was administered except

* The drug regimens were as follows: quinacrine, 2.8 Gm. in seven days (1.0 Gm. the first day and 0.1 Gm. three times a day for six days), 2.2 Gm. in three days (1.0 Gm. the first day and 0.6 Gm. daily for two days); chloroquine, 2.0 Gm. in seven days (0.8 Gm. the first day and 0.2 Gm. daily for six days), 1.0 Gm. in one day, 0.8 Gm. in seven days (0.2 Gm. the first day and 0.1 Gm. daily for six days), 1.5 Gm. in four days, (0.6 Gm. the first day and 0.3 Gm. daily for three days), and 1.5 Gm. in three days (0.9 Gm. the first day and 0.3 Gm. daily for two days); and quinine sulfate, 29.0 Gm. in fourteen days (3.0 Gm. the first day and 2.0 Gm. daily for thirteen days).

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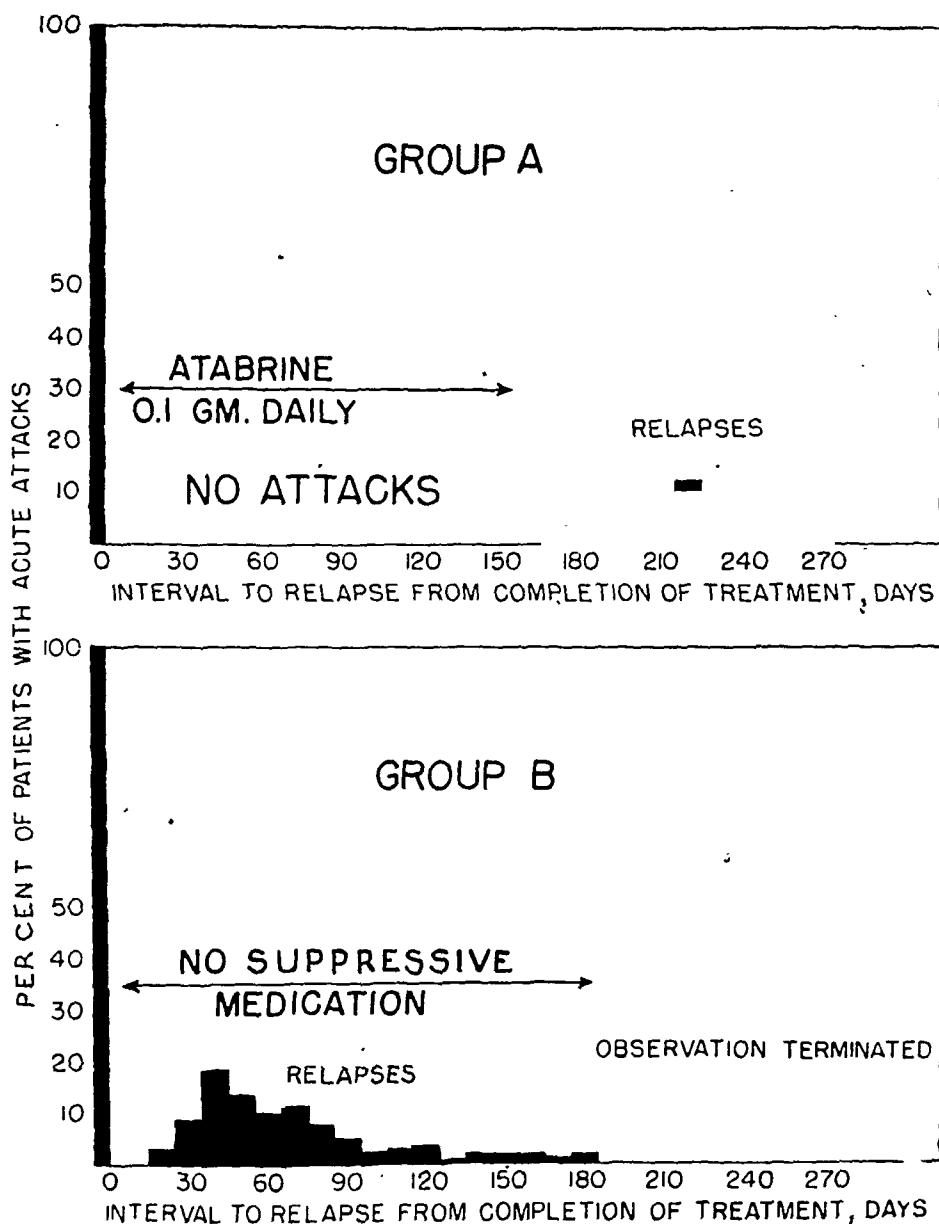


FIG. 1. Distribution of relapses in two groups of patients following treatment for acute attacks of vivax malaria of Pacific origin. Group A was placed on suppression medication 0.1 Gm. quinacrine daily for 150 days after treatment of the acute attack. Group B was treated for the acute attack but did not receive subsequent suppressive medication. Each group was observed for 120 days following the end of antimalarial medication. Note the absence of relapses in Group A during the period of suppressive medication and the similarity in the time distribution of relapses and in the rates of relapse in both groups during the 120-day observation periods.

for treatment of a clinical relapse. A patient was considered to have a clinical relapse when he had a smear positive for malaria parasites in association with an oral temperature above 100°F.

RESULTS

1. *Immediate Effect of Suppression.* During the 150 days of suppression, none of the

forty-nine patients in Group A had either asymptomatic parasitemia or a clinical relapse. The mean of the individual mean fasting plasma quinacrine levels of this group during the five months of suppression was 19 micrograms per liter.

2. *Course of Disease Following Suppression.* During the 120-day period of observation following cessation of suppressive medica-

tion, 82 per cent of the patients in Group A had a clinical relapse. This is nearly identical with the 80 per cent incidence of relapse observed in the 120 day period following treatment without suppression in control Group B. (Fig. 1.) The distribution of relapses in relation to the time following the end of suppressive or therapeutic medication is essentially the same in both groups.

Of ten patients in Group A whom we were able to observe again following treatment for the attack which terminated the first observation period, eight had another relapse within 120 days.

3. *Relationship of Incidence of Recurrence to Number of Previous Attacks.* This relationship is presented in Table I:

TABLE I
RELATIONSHIP OF NUMBER OF PREVIOUS ATTACKS TO INCIDENCE OF RECURRENCE WITHIN 120 DAYS FOLLOWING TREATMENT OF 404 ATTACKS OF PACIFIC VIVAX MALARIA

No. of Previous Attacks	No. Men Treated	Clinical Relapses within 120 Days	
		No. Men	Per Cent
0	116	81	70
1-5	186	135	73
6-10	49	38	78
11-20	40	29	73
21 or more	13	6	46

These data indicate that recurrence at a rate of 70 to 80 per cent in 120 days following treatment with quinacrine, chloroquine or quinine obtains in all groups of patients, except perhaps for a small number who have had a great many previous attacks (over twenty) and in whom the disease may "die out" more abruptly.

DISCUSSION

Our experience with large numbers of patients whom we have treated for acute attacks of Pacific vivax malaria with quinacrine, chloroquine or quinine indi-

cates that approximately 70 to 80 per cent of these patients have a recurrent attack within 120 days.^{3,4} It is reasonable to assume, therefore, that the course of the disease, in the strains of Pacific vivax malaria which we have treated, is one in which 70 to 80 per cent of patients will relapse within 120 days after treatment of an attack with quinacrine, chloroquine or quinine, and that of the patients who have relapsed, 70 to 80 per cent will have still another attack within another period of 120 days following similar treatment. It is generally accepted that vivax malaria dies out usually within two years after the last infection.⁵

Our experience with patients whom we have been able to follow through more than one attack may be cited in further support of the view that recurrence at a rate of 70 to 80 per cent within 120 days is characteristic of Pacific vivax malaria. Of 321 men treated with quinacrine, chloroquine or quinine for acute attacks, 75 per cent relapsed within 120 days. Of these, 120 men were observed again and 70 per cent of them had another attack within 120 days following the previous attack. Of this latter group, thirty-three men were followed for another period of 120 days and 70 per cent of them had a third recurrent attack under our observation.

It is recognized that this characteristic relapse rate of 70 to 80 per cent within 120 days is arbitrary inasmuch as the 120 day observation period was chosen arbitrarily. This period was chosen because it was found to be sufficiently long to include the great majority of recurrent attacks and was found at the same time to be a practical period for study of military personnel. We are aware that not all patients who relapse do so within 120 days, and, accordingly, that not all of the 20 to 30 per cent who do not relapse within 120 days represent complete cures. However, of any large group

treated with quinacrine, chloroquine or quinine, a portion of the 20 to 30 per cent, although it may be small, will have no further relapses. This is supported by the fact that the majority of any large group of patients is cured of the disease within eighteen months after the last infection.

The patients in this study were treated and admitted to the various groups as their attacks of malaria occurred, and no attempt at selection of cases was made. It is believed that this procedure minimized the influence on the rate of recurrence of factors such as differences in the severity of the original infection (i.e., the number of sporozoites introduced into the human host by the infected mosquitoes) and differences between parasite strains which may be responsible for individual variations in the frequency of relapses and in the total duration of the infection.

Our data indicate that the course of recurrence at a rate of 70 to 80 per cent in 120 days applies to patients following cessation of suppression as well as to patients who have been treated for an acute attack without subsequent suppressive medication. Of the ten patients in Group A whom we were able to observe for an additional period of 120 days following relapse, eight had recurrent attacks. Furthermore, nearly all of the malaria patients whom we treated in this hospital had received suppressive medication while overseas. As has been noted, they have followed a course of recurrence at the rate of 70 to 80 per cent within 120 days since the discontinuance of suppression.

The 82 per cent rate of recurrence within 120 days after the 150-day period of suppression demonstrates that complete suppression *per se* does not produce a diminished rate of relapse following the discontinuance of suppressive medication. These data may be interpreted as indicating that complete suppression has not shortened the course

of the disease in these patients, and, indeed, the possibility is raised that such suppression may hold the course of the disease in abeyance and thus may delay complete cure and prolong the duration of the disease in a group of patients. The exigencies of military service did not permit us to continue observation of the suppressed and unsuppressed groups throughout the course of their disease until complete cure of all patients in the groups had been achieved. Consequently, we have no conclusive demonstration that the total duration of the disease in a suppressed group is or is not prolonged.

It must be stressed that our data apply only to complete suppression for 150 days with 0.1 Gm. quinacrine daily in a non-endemic area. It is quite possible that during suppression under less well controlled conditions, the disease will continue to run its course in some patients because of mild attacks permitted by inadequate suppressive medication. Consequently, studies of incidence of attacks in such groups of men may in fact reveal a diminished relapse rate after cessation of suppression. It is conceivable that complete suppression for longer than five months might result in a diminished relapse rate after discontinuance of such suppression, and that complete suppression for as long as two years might eradicate the disease. There is as yet, however, no experimental evidence in support of such effects.

In the absence of conclusive evidence of the effect of complete suppression on the duration of the disease, the routine use of suppressive quinacrine medication for long periods in a non-endemic area seems at present inadvisable, particularly since such medication is not without danger. Serious toxic manifestations in the skin and hematopoietic system (lichen planus and eczematoid dermatitis,⁶ aplastic anemia⁷) occur in a small percentage of individuals who receive prolonged suppressive quinacrine medication. Although the toxicity of chloroquine

administered for many months is not yet clearly defined, it is known that one may encounter toxic reactions on prolonged medication.² The rational use of quinacrine or chloroquine for treatment of acute attacks, however, does not entail similar toxicity. Furthermore, when properly used, these drugs control acute attacks rapidly and permit early return to full activity. So long as the effect of prolonged suppression on the duration of the disease is not clearly delineated and prolonged suppressive regimens may produce toxicity, we believe it is preferable to treat acute attacks in unsuppressed patients rather than to use suppressive medication for long periods.

In the light of the studies and considerations which have been reported here and elsewhere,^{2,3} the following suggestions are made for the management of cases of recurrent vivax malaria of Pacific origin. Acute attacks should be treated with chloroquine or quinacrine. If a patient has had numerous debilitating attacks at frequent intervals since leaving the endemic area, it is suggested that a subsequent attack be treated with the combined quinine-plasmochin or quinine-pentaquine fourteen-day regimens. These regimens have been shown to be curative in a high percentage of cases. Indications, dosage and necessary precautions in the use of these regimens have been presented elsewhere.^{8,9}

It is further suggested that prolonged suppressive medication not be used routinely in a non-endemic area. It should be emphasized that this recommendation is not meant to apply to endemic areas, particularly in time of war when the fighting efficiency of an army exposed to malaria depends on effective suppression. In a non-endemic area, however, suppression is not advisable except in cases of intercurrent illness or in cases in which it is imperative that there be no absence from work during a limited period. Occasionally, it may also be advis-

able in prolonging the interval between recurrences in patients who are suffering from frequent attacks and who cannot spend fourteen days in the hospital as required by the quinine-plasmochin or quinine-pentaquine regimens.

SUMMARY AND CONCLUSIONS*

Quinacrine, 0.1 Gm. daily, was administered to forty-nine patients for 150 days following quinacrine treatment of an acute attack of Pacific vivax malaria. This dose was effective in suppressing completely parasitemia and clinical attacks. In a period of 120 days following termination of suppression, 82 per cent of the men had a recurrence of malaria. This incidence was the same as was found in a control group of sixty-nine men who were observed for 120 days following quinacrine treatment of the acute attack without subsequent suppressive medication. This and other evidence cited indicate that the course of the disease is not shortened by complete suppression and the possibility is raised that the duration of the disease may be prolonged. In the light of the considerations presented in these studies, routine suppression for prolonged periods in a non-endemic area is not recommended.

Recommendations for the management of Pacific vivax malaria in a non-endemic area are made.

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"Muscle Spasm" in Acute Low Back Pain and Similar Syndromes*

A New Method of Treatment with Curare (d-Tubocurarine in Oil and Wax)

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THE entity clinically designated as "muscle spasm" is an integral part of many of the common wear and tear syndromes of every day practice. The term is loosely used but roughly may be defined as a state of transient muscle contraction, not amenable to voluntary control, characterized by resistance to stretch and usually associated with pain on attempted extension.

Clinically, the picture is well recognized. It may be a muscle response to irritation, whether inflammatory or traumatic. It may be reflex in origin and secondary to pathological conditions, visceral or somatic, of like segmental neural connection. Kellgren,¹ Wolff² and others have shown that this latter type of muscle spasm may be perpetuated after cessation of the initiating stimulus and thus present a major treatment problem.

The various lesions which together make up the low back syndrome are excellent examples of the importance of the problem of muscle spasm in treatment. The initiating trauma or etiologic agent is followed by muscle splinting as a protective measure. Pain enhances the splinting or spasm, which in turn is followed by more severe pain and further muscle spasm. The vicious cycle is self-perpetuating. Whether the intense pain is at least partly ischemic in origin is not fully understood.

Dramatic relief may be afforded by any agent which tends to interrupt and break up the cycle of splinting and pain. There are many traditional measures, all of which have some rationale and serve their purpose, at times, admirably. These include heat, traction, ethyl chloride spray, novocaine or saline injections, and heavy sedation. Unfortunately, none of these measures is specific or generally reliable in a series of cases.

Since curare is known to create a myoneural block, it is logical to try to apply its properties to the treatment of muscle spasm. Unfortunately, in aqueous solution its action is evanescent, with poor control of blood levels, and its therapeutic margin is narrow, particularly in the ambulatory or casually observed patient. A newer preparation, tubocurarine in oil and wax,[†] previously described by one of the authors,^{3,4,5} circumvents to a great extent these therapeutic limitations by providing slow absorption at fairly predictable levels of saturation. In previous reports, it has been shown that with this preparation it is possible to create a partial block at the myoneural junction without loss of voluntary function or any unpleasant curare side effects.

The series of cases presented in this paper has been treated with the aforementioned

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TABLE I

ACUTE LOW BACK DISORDERS OR SIMILAR SYNDROMES

I. Associated with structural abnormalities, such as osteoarthritis and congenital or acquired deformities.

Name	Diagnosis	Symptoms and Signs	Previous Treatment	Response to Curare	Reaction
H. H.	Acute low back strain, sacralisation L ₅ with osteoarthritis	Severe low back pain Marked splinting Loss normal lordosis	Traction Heat Morphia	Complete relief of diffuse severe pain with muscle relaxation in 2 hrs. Pain now localized to L ₅ body on movement only	None
L. T.	Kyphosis and scoliosis upper thoracic spine	Constant pain and aching with muscle spasm T ₄ region and spinatus group	Massage	Relief of pain and aching discomfort	Diplopia 1½ hrs.
H. S.	Osteo arthritis spine with acute low back strain	Severe generalized low back pain with immobility, some sciatic radiation	Diathermy Static wave	Relief of severe pain Residual soreness Loss sciatic pain	Dizziness 2 hrs.
C. D.	Unstable back with sacralisation L ₅ , acute low back strain	Loss lordosis Immobility of back Severe generalized pain	Ethyl chloride Heat	Subsidence of generalized pain, residual aching in sacral region	Diplopia 1 hr.
L. R.	Lumbosacral osteoarthritis with scoliosis. Degenerative disease of the intervertebral disc with narrowing	Weak back for years Severe low back pain 2 months with occasional radiation to rt. leg	Heat	Relief of severe pain in 2 hrs. Slight soreness low back	Drowsy next day
E. Y.	Osteoarthritis cervical spine with cervical 'myositis'	Splinting trapezii, erector capiteae Lack of mobility of head and shoulders	Heat Massage	Relief of pain Marked increase in mobility. Residual soreness	None
L. M.	Infarct vertebral body L ₄ (sickle cell)	Splinting lumbosacral muscles with immobility and severe pain	Heat Bedboards	Reduction of spasm, able to move about, pain localized to site of pathology	None
H. S.	Acute low back strain, osteoarthritic changes with degenerative disc disease and narrowing of lumbar interspaces	Severe generalized pain with marked lumbo-sacral tilt, immobility of lumbar spine	Heat Corset Massage	Relief of generalized pain, increased mobility	Diplopia 1 hr.
E. S.	Osteoarthritis cervical spine with spurs	Severe neck and shoulder girdle pain, limitation of movement, headache	Diathermy Massage	Relief of constant pain and headache in 2 hrs. Residual soreness, increased mobility	None

II. With no demonstrable structural abnormalities,

K. K.	Acute low back syndrome	Severe lumbosacral pain with tilt to right Loss of lordosis, left sciatic pain, immobility	Heat Morphia	Dramatic relief in 3 hrs. of sciatic and low back pain Residual soreness	None
H. B.	Autonomic disturbance with trapezius, erector capiteae and shoulder girdle muscle spasm	Severe neck and shoulder pain radiating down arms. Immobility of neck	Morphia Heat Massage	Marked relief, residual soreness	None

TABLE I (Continued)

Name	Diagnosis	Symptoms and Signs	Previous Treatment	Response to Curare	Reaction
III. Following operation for removal of herniation of nucleus pulposus.					
H. B.	Post-op. herniated nucleus pulposus with low back syndrome, recurrent, and pyelitis C	Severe erector spinae spasm with complete immobility of low back and generalized pain	Heat Morphia Massage	Increase in mobility Loss of excruciating pain, residualsorenessmarked	None
H. H.	Post-op. laminectomy for herniated nucleus pulposus	Excruciating generalized low back pain; immobility of spine, loss lordosis	Corset Heat Novocaine Morphia	Dramatic complete relief in 2 hrs. Able to move about freely, soreness in muscles of low back	None
J. G.	Post-op. herniated nucleus pulposus Recurrent pain and muscle spasm of glutei and paravertebral muscles	Immobility, generalized low back pain	Heat Bedboards Massage	Relief generalized pain, increased mobility, 'pain now in bones'	Diplopia few minutes
IV. Associated with nerve root compression.					
D. W.	Herniated nucleus pulposus narrowing of interspace	Low back pain, ? sciatic radiation, and abdominal distention	Morphia Traction Bedboards	No relief, accentuation segmental distribution of sciatic pain	None

curare suspension, usually after conventional methods have failed. It has been consistently possible to break up muscle spasm and enhance recovery rate when the initiating pathological condition is static or brought under control. Where the pain and local muscle spasm were secondary to a continuing stimulus, i.e., root compression, radicular pain persisted after reduction of the spasm and the local or reflex spasm often recurred shortly. This response may prove to be a useful diagnostic test and will be discussed later in the paper.

The cases studied run the gamut of low back disorders, including the usual orthopedic disturbances, so-called low back strain, osteoarthritis of the spine, actual vertebral lesions, disc lesions and also some instances showing reflex spasm secondary to remote disease. Table I is a compilation of typical cases and results.

It is apparent from a perusal of the above data that in many cases of low back syn-

drome an abrupt cessation of the major complaints often follows upon relief of muscle spasm. The sequence of events after treatment is of interest. The patient usually notes an abrupt relief of major pain within several hours after injection. Mobility is increased and the patient often describes a feeling of pleasurable relaxation, even drowsiness. The severe pain is followed by muscle soreness and localized pain in the region of actual disease, if it is capable of local signature. The soreness is a logical sequel, since protracted muscle contraction is associated with diminished vascular exchange and ischemia. It is known that, depending upon the chronicity of the process, the muscle involved may thus show reversible inflammatory changes, cloudy swelling, etc. The characteristic tenderness which remains even after complete relief of pain seems to have its basis in this transient pathologic state.

Three case histories are described in detail since they are representative of the general results:

CASE REPORTS

CASE I. H. H., a forty-eight-year old male, member of a medical college faculty, over a period of years has had occasional lumbosacral pain with moderate muscle spasm. These attacks were self-limited and disappeared without residue. In recent years, the patient had grown much heavier and had led a more sedentary existence. In February, 1946, he began to note recurrence of lumbosacral pain. This became increasingly severe over a period of days and he was admitted to the hospital. On mild sedation, bed boards and rather haphazard traction, he improved enough in three days to be discharged. X-ray examination had revealed an unstable lumbosacral joint with proliferative arthritis in the joint region.

Two days later pain had increased to its former severity and the patient was again hospitalized. Muscle spasm at this time was more pronounced, and the patient was in constant severe discomfort in all positions. Traction was reinstituted without relief. Morphia and sedation were used in large doses. The orthopedic consultant advised a body spica, full length, and this was applied. The patient complained more and more bitterly, remained sleepless and unrelieved by any form of medication. At the end of four days, spinal anesthesia was contemplated in a heroic attempt to reduce the marked muscle spasm of the entire low back region with the accompanying severe pain. A trial of curare in oil was agreed upon instead. One cc. of the suspension was given in the right buttock. Two hours later, the patient stated that his back muscles had relaxed and at the same time the accompanying generalized pain had vanished. The reduction in muscle spasm was immediately demonstrable on examination. The patient now noted only focal pain on motion at the lumbosacral articulation. Relief of pain was followed by adequate rest without medication. The patient became less tense, began to eat and regain his normal equilibrium. However, by the third day, in dread of a recurrence, he

requested a second injection. The same dose of drug was given at this time and again three days later. The spasm never recurred and the patient's subsequent convalescence was completely uneventful. A back brace was prescribed by the orthopedist and when this was fitted, the patient was allowed up and discharged from the hospital.

CASE II. K. K., a fifty-year old woman, was admitted as an emergency because of excruciating low back pain with left sciatic radiation. She was unable to move about without evoking showers of pain throughout the lumbosacral region and down the left leg. She lay in bed with the low back characteristically immobile, and the left leg supported on pillows at the knee. Examination was impossible because of the extreme pain and x-ray examination could not be carried out. Conventional medication afforded minimal relief. One cc. of *d*-tubocurarine in oil was injected in the left gluteal region and in two hours the patient had noted an almost complete cessation of pain. She was able to move about and physical examination and x-rays were performed. There was no evidence of nerve root compression on examination. X-rays showed normal low back structures but an arthritic process about the hip joint. As the pain and muscle spasm of the low back diminished, the sciatic reference of pain gradually disappeared. Within three days, the patient was up and about her room and shortly was discharged free of symptoms.

CASE III. D. W., a fifty-four year old male, had had recurrent attacks of low back pain since he lifted a heavy weight some time ago. On admission, he complained of severe lumbosacral pain with radiation to the right knee. When standing, his posture was stooped, with the low back immobile and the right leg flexed protectively at the knee. There was marked splinting of the erector spinae muscle group. On traction, heat and bed boards, he developed abdominal distention of such degree that intubation was necessary. Prostigmin and pitresin afforded no relief. In the hope that curare might reduce his low back signs and therefore ameliorate the reflex distention, he was given 0.9 cc. of *d*-tubocurarine in oil and wax, intramuscularly. Coincidentally, and with vigorous treatment, the distention was relieved.

After curare, the patient noted definite sciatic distribution of pain on coughing and sneezing and the segmental nature of his leg pain became objectively more evident. At operation, subsequently, a large protruded herniation of the nucleus pulposus was found at the fourth lumbar interspace on the right.

These cases are cited to delineate the value of the response to curare therapy as a diagnostic test. As described above, relief of muscle spasm ordinarily is followed by abrupt relief of local pain and its reference. However, where root compression, such as in herniation of the nucleus pulposus, is the exciting and continuing stimulus, the relief of local muscle spasm does not influence the severe pain and actually may highlight its segmental nature by removing temporarily the purposeful splinting action of the muscle spasm.

Several cases are included in Table I in which the pathological process is very similar but of different anatomical distribution. Where the same criteria are met, the results are much the same. However, it should be stressed that muscle spasm of the erector capiteae and trapezius groups is more difficult to treat, since these muscles are seldom out of use and unless specifically prescribed, are difficult to put at rest. Strict bed rest is of major importance to successful therapy.

Among all the pathological entities which may be classified as "wear and tear" syndromes, rheumatoid arthritis seems the most refractory to treatment. There are few, if any, specific therapeutic measures. It has seemed worth while to evaluate the effect of curare in the acute phase of the disease, since to the clinician at this stage there are changes similar to skeletal muscle spasm. The authors are fully aware of the danger involved in the indiscriminate use of the term "muscle spasm." So far as the aforementioned conditions are concerned, the entity is clear-cut. In rheumatoid arth-

ritis there is a very similar clinical picture, arising perhaps out of different mechanisms. Several factors are at play. In addition to joint inflammation, there may be infiltration of the actual muscle mass by inflammatory exudate. Freund et al.⁶ have described lymphorrhagic infiltrations in the peripheral nerves. All these irritative phenomena apparently either directly or reflexly give rise to the extreme pain on attempted stretch or attainment of full range of motion.

The typical protective position adopted in an attempt to prevent pain is a major cause of deformity, reversible early but static in the later stages of the process. Long periods of fixation, with unwillingness to perform normal movements because of intense pain, lead to atrophy of disuse and fibrosis.

The clinical goal is, first the prevention of long standing protective splinting with subsequent muscle changes and disturbances of joint function, and secondly, the alleviation of pain. In early cases, it has been routinely possible to influence favorably the characteristic flexion deformity during the period of treatment. Pain in these cases is based upon a complex combination of factors, but with relief of abnormal muscle tension there seemed to be a gratifying diminution in pain. Major forms of analgesia could be discontinued and the residual pain controlled well with traditional medication such as aspirin.

The following case reports illustrate the type of disorder amenable to treatment and the therapeutic results obtained.

CASE IV. E. S., a twenty-five-year old woman, suffered with severe rheumatoid arthritis for six months. On admission her sedimentation rate was markedly elevated and agglutination with hemolytic streptococcus group A was positive. Flexion contracture of both elbows was present with extension possible only to 110 degrees, with severe pain supervening beyond this range. Her fingers were characteris-

tically fusiform. The patient was admitted to the hospital partially curarized over a period of four days with 1 to 1.1 cc. of *d*-tubocurarine in oil and wax daily. After saturation with drug, her elbows could be extended completely without pain. She was given two transfusions with whole blood, gold therapy was started, and she was discharged to the clinic where curare was continued twice weekly and later weekly. Exercise was encouraged. At the present time she is free of pain, has complete extension of elbows and knees and sleeps soundly. She is ambulatory, carries out her housework and drives a car. Of interest is the fact that she has very little atrophy of the small muscles of the hand at present. During the course of treatment she noted slight drowsiness on several occasions and diplopia momentarily on one occasion.

CASE V. D. D., a male of thirty, had had an acute onset of peripheral joint and back pain two months before admission. One year and again four months previously, he had been treated successfully for gonorrheal urethritis. At another hospital massive quantities of penicillin had been injected intramuscularly and into a knee joint without benefit to his present complaints. On admission he was in marked distress with flexion contractures of both elbows to 85 degrees and of both knees to 100 degrees. These could be overcome passively only very slowly and with much pain to the patient. Spine x-rays showed changes in three of the apophyseal joints of the lumbar spine and in the right sacroiliac joint. Examination of the peripheral joints showed no heat, redness or swelling, and x-rays were negative. The patient ran a fever of 101°F. daily and for four days was treated with analgesics. Pain remained severe and sleep was very poor on 200 to 250 mg. of demerol daily. He was started on 1 cc. of *d*-tubocurarine in oil and wax daily and by the third day pain could be well controlled with aspirin and codeine. He was able to extend his arms and legs actively. Partial curarization was maintained and he was started on x-ray therapy, on which treatment he showed a marked exacerbation of symptoms. During curare treatment, the patient noted double vision on one occasion for about thirty minutes, but no other side effects were encountered.

In recognition of the difficulty in assaying therapeutic results in rheumatoid arthritis, the apparent beneficial effect of curare must be interpreted with caution. However, results are sufficiently encouraging to warrant extension of the present study. An attempt is being made to support clinical impressions by objective measurements. It is hoped that a larger body of cases with objective correlative data can be reported at a later date.

SUMMARY

In an attempt to exploit the physiological properties of curare in the treatment of muscle spasm, a new preparation has been used. This preparation, *d*-tubocurarine in oil and wax, because of its slow absorption affords a much more satisfactory therapeutic index and a more prolonged effect than the aqueous solution. A series of cases in which patients with true muscle spasm were treated is described, and in addition a small group with a similar clinical picture but of possibly different origin is included.

CONCLUSIONS

1. "Muscle spasm" is often an integral part of the clinical picture of the acute low back syndrome.
2. Striking relief of symptoms in "low back" and similar syndromes may follow alleviation of muscle spasm.
3. A suspension of *d*-tubocurarine in oil and wax has proven very useful in breaking up the muscle spasm present in the conditions.
4. The difference in the response of patients exhibiting root compression from those with other types of disorders is described, and is suggested as a diagnostic test.
5. The use of *d*-tubocurarine in oil and wax for the prevention of deformity and alleviation of pain in early rheumatoid arthritis has led to promising results in a small group of patients.

6. On the basis of the clinical results so far obtained, it is believed that further exploration of this form of therapy is warranted.

The authors wish to express their obligation to the Attending Staff of the Columbia-Presbyterian Medical Center for the opportunity to study many of the cases presented in this series, and, in particular, to the late Dr. Clement B. Masson, whose unflagging interest and cooperation had much to do with making this work possible.

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Subacute Bacterial (Streptococcus Viridans) Endocarditis Treated with Penicillin*

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IT has been only about three years since a patient with subacute bacterial endocarditis was an unfortunate object who had no hope, served no purpose other than to contribute his physical signs to the teaching of physical diagnosis, and finally his viscera to the study of gross and microscopic pathology. However, in this brief interim the use of penicillin has provided interest, animation, and, indeed, life itself to the majority of these individuals. There have been reports of a number of cures. Chief among these are the series of Dawson and Hunter,^{1a} Loewe,² Loewe, Rosenblatt, Greene and Russell,³ Bloomfield and Halpern,⁴ Meads, Harris and Finland⁵ and Bloomfield, Armstrong and Kirby.⁶ Many other isolated cases and small groups of cases have also been recorded. Although the disease is not rare, it does not occur commonly enough to produce series involving large numbers of cases. Thus conclusions must be drawn from smaller multiple series, and it is therefore important that many reported series be carefully studied not only from the standpoint of the cures effected but also from the standpoint of failures encountered.

As in all diseases, early diagnosis and treatment are of paramount importance. Noteworthy in these and other published data is the unduly long period of time elapsing between the onset of symptoms, diagnosis and treatment. This period averaged fourteen and one-half weeks in this

series. In spite of the high recovery rate, however, the occurrence and persistence of cardiac insufficiency following the infection and recovery gives the impression that this complication might have been obviated by earlier diagnosis and treatment. A presumptive diagnosis of subacute bacterial endocarditis should always be made in any patient having a heart murmur in conjunction with any one of the following: Chills, fever, emboli, splenomegaly, clubbed nails, hematuria or repeated pains in the back. A positive diagnosis may be made with a combination of the above plus the finding of *Streptococcus viridans* upon repeated blood cultures. Blood cultures should be taken twice or three times each day over a period of three or four days. This is important because it has been noted that positive cultures may be obtained either when the temperature is low or high. Cultures should be planted in blood agar plates and liquid media both aerobically and anaerobically, since different strains of *Streptococcus viridans* may be aerobes, anaerobes or facultative anaerobes. It is of exceptional interest to note that one of this series (no. 35749) was referred because of rheumatic heart disease with congestive heart failure, and although he at no time had any fever or leukocytosis, was found to have an enlarged spleen. This in conjunction with the heart murmur satisfied the requirements for a presumptive diagnosis of bacterial endocarditis. In all, nine blood cultures were

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made during three successive days. All were sterile except numbers 3, 5 and 9. These cultures showed from eleven to twenty-two colonies of *Streptococcus viridans* per cc. of blood. Obtaining blood cultures in this manner obviously will save time and add to the accuracy of the diagnosis. Early recognition and treatment might possibly obviate the occurrence of a fatal or crippling cerebral or other embolus and might indeed mean the difference between the success or failure of treatment.

This group of patients exhibited a clinical feature which has been outstanding in almost all patients with subacute bacterial (*Streptococcus viridans*) endocarditis which I have observed. In practically every instance these patients are perfectly willing to undergo any hardship in order to recover. I have never observed a patient with this disease who has not cooperated cheerfully and accepted any proposed treatment, from multiple needle punctures to artificial fever. This characteristic seems to be as typical in this disease as embolic phenomena or any of the other clinical or laboratory aspects. Bacterial endocarditis has not been proven where lack of cooperation, psychoneurotic tendencies and unwarranted complaining have been present in a suspected patient.

As yet there is little conclusive data as to the exact manner in which the lesions heal. Since there is practically no blood supply in the diseased valves, other than those involved by syphilis,⁷ it seems only logical that the constant bathing of the vegetations by penicillin brings about healing by gradual penetration from the surface of the lesions. This would explain the necessity for prolongation of treatment until the vegetations have healed to their bases. The pathological findings in two patients who had healed subacute bacterial endocarditis lesions were reported by Rosenblatt and Loewe.⁸ Healing with endothelialization of the diseased valves was noted. These

patients died as the result of congestive cardiac failure several months after treatment. Cultures of the valves and adjacent myocardium were found sterile.

Congestive heart failure was a prominent cause of death in the majority of reports setting forth the mode of death, both before and since the advent of penicillin. It occurred in eight instances or 67 per cent of this series. In the eight of the eleven patients cured of their lesions but who died with congestive heart failure, seven or 88 per cent showed marked improvement from the standpoint of cardiac insufficiency after treatment with penicillin. Therefore, these findings indicate that one is not justified in presuming the ultimate disability to be so great as to warrant depriving any individual of treatment. Early and vigorous management of cardiac failure has probably contributed to the success of this series.

In vitro studies are important. It has been shown by Ellard Yow and his associates¹⁰ that these laboratory procedures are a reliable guide in determining the type of antibiotic which is best suited for the bacterium involved. Unfortunately, some strains of *Streptococcus viridans* are not inhibited by penicillin, even in high concentration. In this series all strains of *Streptococcus viridans* were found to be sensitive to penicillin in a dilution of 1 unit per cc. These authors point out that blood levels higher than 0.1 unit per cc. are but very rarely obtainable. Subsequent *in vitro* studies have been conducted with penicillin dilutions of 1.0, 0.1 and 0.05 unit per cc. These more nearly approximate expected blood levels in patients.

From Table I it is learned that the total dosage of penicillin varied greatly, especially in those treated early in the series at which time there was no standard procedure, penicillin was available only in very limited quantities, and the dosage was often quite small. Indeed, there is no fixed

TABLE I
SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS *

Case Number...	25818	31234	35749	34932	City Hosp.	38396	39286	39748	38514	39242	43933	36529
Age.	40	9	30	22	68	42	4	51	21	4	24	28
Sex.	Male	Male	Male	Female	Female	Male	Female	Male	Female	Male	Female	Female
Basic lesion.	Rheumatic mitral stenosis	Patent inter-ventricular septum	Rheumatic mitral stenosis, aortic regurgitation	Mitral stenosis, rheumatic	Rheumatic mitral and aortic regurgitation	Rheumatic mitral stenosis, aortic regurgitation	Patent inter-ventricular septum	Aortic stenosis, mitral stenosis, rheumatic	Patent ductus arteriosus	Patent ductus arteriosus and other congenital defects	Patent ductus arteriosus	Aortic insufficiency, mitral stenosis, rheumatic
Duration of illness before treatment.	7 weeks	4 months	No symptoms, palpable spleen only	4 weeks	5 weeks	5 months	2 months	7 months	6 months	6 weeks	4 months	3½ months
Infecting bacterium.	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>	<i>Streptococcus viridans</i>
Complications. . .	None	Pulmonary infarcts, cardiac insufficiency	Cardiac insufficiency	Endocarditis began 10 days after normal delivery	Cardiac insufficiency	Cardiac insufficiency	None	Duodenal ulcer, cardiac insufficiency	Pulmonary infarctions, mild cardiac insufficiency	Cardiac insufficiency, pericardial effusion	Pulmonary infarctions, mild cardiac insufficiency	Congestive failure, ruptured aortic cusps mycotic aneurysms
Embolic phenomena.	Generalized small	Lungs, spleen and generalized	Spleen, kidneys, finger tips	Multiple petechia in skin	None	Spleen, kidneys, generalized	None	Spleen, kidneys	Spleen, kidneys, fingers	Kidneys, spleen, generalized	Lungs, spleen kidneys, generalized	Multiple at outset none after cultures negative and temp. normal
<i>In vitro</i> studies. . .	Inhibited by penicillin not by sulfonamides	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Cultures obtained elsewhere	Inhibited by penicillin	Cultures obtained elsewhere	Inhibited by penicillin at outset, but later only in concentration greater than 1 u. per cc.	Inhibited by penicillin	Inhibited by penicillin
Treatment.	Penicillin 5,000,000 units 21 days, I.M.	Penicillin (a) 2,050,000 units 20 days, (b) 2,000,000 units 20 days, I.M. drip	Penicillin 3,150,000 units 14 days, I.M.	Penicillin 3,335,000 units 21 days, I.M.	Penicillin 5,200,000 units 22 days	Penicillin 4,000,000 units 20 days, I.M.	Penicillin 4,885,000 units 42 days, I.M.	Penicillin 3,520,000 units 15 days, I.M.	Penicillin (a) 400,000 units 4 days, (b) 600,000 units 6 days, (c) 1,000,000 units 10 days, (d) 2,000,000 units 20 days, (e) 4,200,000 units 21 days. Total 8,200,000 units 61 days	Penicillin 6,980,000 units 43 days, Para-amino-hippuric acid 8 days	Penicillin (a) 600,000 units 6 days, (b) 2,000,000 units 20 days, (c) 2,000,000 units 20 days, (d) 5,000,000 units 21 days. Total 9,600,000 units 67 days	Penicillin 6,250,000 units 25 days
Sequelae.	None	None	None	None	None	None	None	Subdeltoid bursitis	Excision of ductus arteriosus	Congestive heart failure	Excision of ductus arteriosus	Cardiac failure bacterial lesions healed
Blood cultures sterile.	24 hours	24 hours	12 hours	4 days	12 hours	12 hours	24 hours	12 hours	24 hours	42 days	24 hours	24 hours
Cause of death.
Result follow-up.	Cure 24 months	Cure—no cardiac insufficiency 22 months	Cure—slight cardiac insufficiency 19 months	Cure 19 months	Cure—cardiac failure markedly improved. 17 months	Cure—no cardiac insufficiency. 16 months	Cure 15 months	Cure 15 months	Cure 14 months	Cured—definite cardiac failure, cultures sterile. 13 months	Cure—murmurs and thrill gone. 12 months	Cure bacterial lesions healed Died—10 weeks after cultures sterile

* Recapitulation of twelve cases of subacute bacterial (*Streptococcus viridans*) endocarditis.



FIG. 1. The margins of the aortic cusps are rolled and thickened. The surfaces are glistening and free of vegetations or other active inflammatory changes. Probes are in place through the four perforations of the valve cusps. These perforations resulted from mycotic aneurysm formation. Marked hypertrophy and dilatation of the left ventricle are evident.

standard procedure today. There seems to be general agreement, nevertheless, that a minimum treatment period of six to eight weeks, employing a daily dosage of 250,000 units of penicillin is desirable. When one considers the deep seated implantation of the bacteria in the vegetations, the advisability of prolonged treatment becomes obvious. The failure of sulfonamides and other bacteriostatic agents to penetrate these lesions in many cases probably has accounted for their failure in most instances. Meads⁹ has pointed out the urgency of giving adequate dosages of penicillin in any type of infection which might be susceptible to this agent. Therefore, the total daily dosage should be increased in the event of continued positive blood cultures or fever, and the time interval shortened as the case demands.

Other matters of importance are blood transfusions, adequate nutrition, general hygienic care, and, when practicable, the elimination of focal *Streptococcus viridans* infection. This type of infection has been

found principally about the teeth and gums, and is best managed while the patient is still maintained on a full blood concentration of penicillin. If gingivitis of appreciable degree exists along with dental caries, extensive dental extractions should be performed. This has resulted in negative blood cultures in one patient who previously had exhibited occasional positive cultures during the course of her therapy.

The following series (Table 1) embraces twelve cases of proven subacute (*Streptococcus viridans*) endocarditis treated with penicillin. All have been followed for from twelve to twenty-four months. Of these eleven (or 92 per cent) are still alive and well. A number of patients have been treated since but have not been observed over a sufficient period of time to warrant reporting at this time. Heparin or other anticoagulants were not employed in any of these cases.

One patient (34932) developed a recurrence of her *Streptococcus viridans* infection and the classical picture of subacute

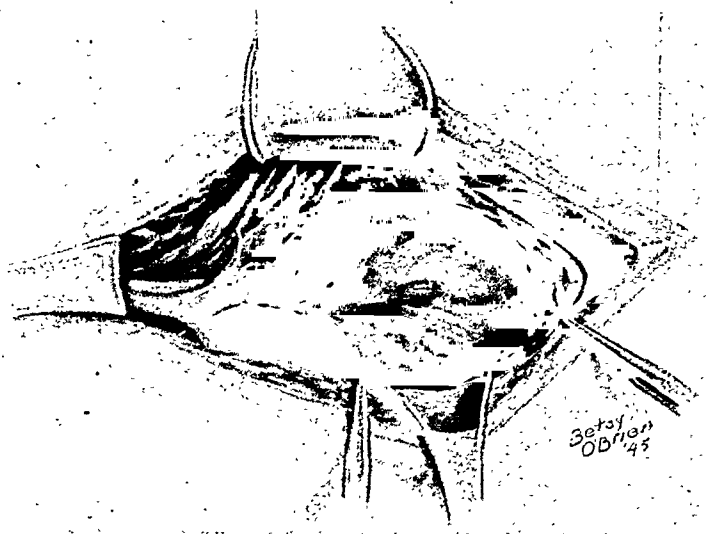


FIG. 2. Drawing at operation of the mycotic aneurysm of the right popliteal artery.

bacterial endocarditis with multiple emboli. The organisms recovered in blood cultures were found to be sensitive to penicillin *in vitro*, and penicillin therapy resulted rapidly in a good clinical response and negative blood cultures. She was free of fever and clinically well three months after treatment of the second infection.

An autopsy was performed on one of the twelve who expired (36529) and death was found to be due to congestive cardiac failure and pneumonitis. At the time of her original admission she showed frank evidence of perforation of the aortic valve in the form of a grade v or vi "base violin string type" of diastolic murmur along the entire sternum and an accompanying pronounced diastolic thrill. As noted in Table 1, the cultures were free of *Streptococcus viridans* within twenty-four hours after penicillin was instituted, and they remained so for ten weeks. Furthermore, the sedimentation rate was normal. The added factor of cardiac failure brought about by left ventricular strain as the result of the multiple perforations in the aortic cusps was the most direct cause of death. Pathologic findings showed chronic mitral and aortic rheumatic valvular disease with no evidences of remaining *Streptococcus viridans* infection. The perforations in the

aortic valve are illustrated in Figure 1. A further interesting complication was a mycotic aneurysm of the right popliteal artery, which was excised after penicillin therapy was started. (Fig. 2.)

DISCUSSION

Twelve patients with subacute bacterial (*Streptococcus viridans*) endocarditis which have been treated with penicillin are presented. Eleven (or 92 per cent) are alive and well from twelve to twenty-four months after treatment. Pertinent data are summarized in Table 1. Anticoagulants were not employed.

The success of the treatment of subacute bacterial endocarditis lies first in early diagnosis, which is hastened and confirmed by obtaining blood cultures three times daily for three successive days; second, in prolonged treatment with penicillin in adequate dosage; third, management of the cardiac failure; fourth, employment of general measures, especially blood transfusions and replacement of serum proteins; and fifth, in the use of *in vitro* studies which are of inestimable value in prognosis and in governing the course of therapy.

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Folic Acid and the Bone Marrow in Radiation Therapy*

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FROM October, 1942, to July, 1946, 191 cases of lymphoblastomas were observed. This group included giant follicular lymphoblastoma, lymphosarcoma, reticulum cell sarcoma and Hodgkin's disease. The bone marrow studies revealed in all instances a marked depression of the myelopoietic and erythropoietic systems. The normal myeloid-erythroid ratio varied between 2:1 and 8:1 and the myeloid-lymphoid ratio 5:1. It was noted that the decrease in the myeloid-erythroid elements was of a depressed type with the ratios more or less constantly maintained, whereas the myeloid-lymphoid ratios were almost completely reversed, i.e., 0.5:5. These features were observed consistently when the bone marrow was studied on admission. It was assumed that these effects were due primarily to the overactivity of the reticulo-endothelial system in these diseases. These bone marrow effects were reflected in the peripheral blood by a marked anemia and neutropenia with an increase in the lymphocytic elements. In the lymphoblastomas this cytophagic and hormonal (?) depressant effect on the bone marrow would seem to be rather comparable to the depressant effects seen on these structures in primary splenic neutropenia, thrombocytopenia, splenic pancytopenia and Felty's syndrome.

When radiation therapy was introduced in the treatment, the anemia and neutropenia became progressively more severe necessitating on the average daily to weekly transfusions of red cells or whole blood in

order to maintain, as closely as possible, the red cell, hemoglobin and neutrophilic levels within normal limits. These depressant and destructive effects on the bone marrow elements are believed to be due to a combination of the excessive cytophagic activity of the reticulo-endothelial system in these diseases and the destructive effects of radiation.

There were 122 cases given routine radiation therapy accompanied by transfusions. In all of these cases the average length of hospitalization was nine and eight-tenths months with a range from five to thirteen months. The radiation reactions and the general depressant effects were severe. The bone marrow and peripheral blood remained continually abnormal. The sedimentation rates decreased slowly but never returned to normal. The stress on blood bank, donors, laboratory and hospital personnel consequent to maintaining a semblance of hematologic equilibrium in these patients during radiation therapy was profound. These factors were so formidable that an adjunct to this therapy was sought. Beginning January, 1944, the Lederle Laboratories, through the courtesy of Doctor Thomas Jukes, supplied liberal quantities of folic acid. This was supplied in bulk powder and in capsule form so that large dosages could be given routinely ranging from 75 to 150 mg. three times daily. Considerable counsel and aid was given by Dr. Daft and Dr. Sebrell of the National Institute of Health, Washington, D. C.

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There were seventeen patients treated with large doses of folic acid without any other therapy. There was no demonstrable beneficial influence on the course of the disease. Subsequently these cases were given radiation therapy.

There were sixty-nine patients treated with radiation therapy, transfusions and folic acid. When folic acid was added to radiation therapy, it was noted that the patients withstood radiation therapy better, with less nausea, vomiting and general depressing physical effects. The sedimentation rates returned less slowly to normal. The necessity for red cell or whole blood transfusions decreased in frequency to an average of one in eighteen days. The average time of hospitalization was reduced from nine and eight-tenths months to five and three-tenths months with a range from three to six months. The bone marrow on discharge showed an increase in the myeloid and erythroid elements and the myeloid-lymphoid ratios tended to return to normal although they never reached normal.

SUMMARY

There were 122 patients with lymphoblastoma treated with radiation therapy and transfusions. The depressant effect on the bone marrow by the disease and therapy was profound.

Seventeen patients were treated with folic acid alone without any demonstrable effect on the course of the disease.

Sixty-nine patients were treated with folic acid in addition to routine therapy. The addition of folic acid seemed to decrease the deleterious and depressant effects of radiation therapy on the bone marrow, decrease the necessity for as frequent transfusions, shorten the period of hospitalization and seemed to have some beneficial influence on the course of the disease during radiation therapy.

CONCLUSION

Folic acid is recommended as a useful adjuvant in maintaining the hematologic well-being of patients receiving massive and prolonged radiation therapy.

Clinical Vibrometer*

An Apparatus to Measure Vibratory Sense Quantitatively

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THE clinical signs of peripheral neuropathy result from an interruption in the transmission of impulses in both sensory and motor fibers. The more common sensory stimuli used for detecting

the existence of a neuropathy consist of those necessary to elicit pain, touch, sensation of heat and cold, and vibration sense. It is well known that the more profound the disease, the greater the stimulus necessary to elicit a response in any of these sensations. Thus it would appear that any method which could quantitatively measure the threshold of the response to a stimulus would serve as a more satisfactory criterion for clinically evaluating the intensity of disease than if one were compelled to resort to conclusions based upon crude clinical perceptions.

It appears that one of the earliest functions to be disturbed in peripheral neuritis is that of vibration sense. The determination of impairment in vibratory sense may, therefore, serve as a function of impairment in the transmission of other impulses. In order to estimate quantitatively the degree of impairment in vibratory sense, one may use a vibrating instrument in which either the frequency of vibration or the amplitude of vibration can be altered.^{1,2}

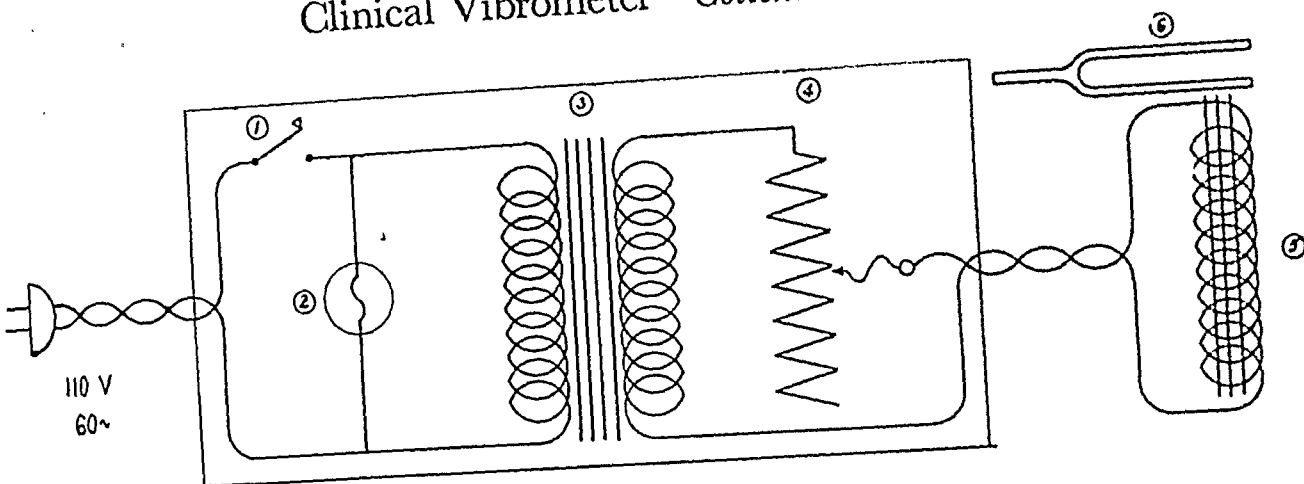
We have devised a simple apparatus for estimating degrees of impairment in vibration sense by electrically activating a tuning fork which has the property of varying the amplitude of vibration while keeping the frequency constant.

This apparatus consists of a tuning fork, carrying an electromagnet on one tine, the other tine serving as the pole piece. The electromagnet is energized by a current



FIG. 1. Clinical vibrometer in use.

* From the Departments of Metabolism and Medicine of the Israel Zion Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York.



- 1 On-Off Switch
- 2 Pilot Light
- 3 Transformer
- 4 Rheostat
- 5 Electromagnet
- 6 Tuning Fork

FIG. 2. Wiring diagram for clinical vibrometer.

obtained from a 60 cycle power line. The usual 110 volt current is reduced through a transformer to 6 volts. The intensity of the current is controlled by a wire-wound rheostat. The amplitude of vibration is controlled by the rheostat which has a calibrated circular dial. The calibrations are in arbitrary units from 100 to 0, which permit duplication of any desired setting. (Fig. 1.) The wiring diagram is seen in Figure 2.

Rotating the indicator from 100 to 0, reduces the resistance in the rheostat, thus allowing for a greater amplitude of vibration in the tuning fork. We arbitrarily set the scale so that when the indicator was at 100, the amplitude of vibration was so minimal that the normal subject could just barely detect it.

We found that the normal subject was thus just able to detect vibrations produced with the resistance dial set at 90 or more, up to 100. We also found that patients who

had an impairment in vibratory sense, responded to those higher amplitudes of vibration when the resistance dial was below 90. There appeared to be a direct relationship between the degree of impairment in vibratory sense and the amplitude of vibration to which the patient responded. Thus as vibratory sense was found to be more impaired, responses were initially perceived only to such high amplitudes as were detected by the lower figures on the dial.

CONCLUSION

An apparatus is described for quantitatively measuring vibration sense.

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Impaired Vibratory Sense in Diabetes*

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PERIPHERAL neuritis is one of the most common complications of diabetes. In spite of its clinical importance, no procedure employed in the traditional neurological examination has offered the physician an opportunity to obtain a satisfactory concept of the intensity of involvement of the peripheral nerve. The

vibrometer which we have described in the previous article makes it possible to quantitate the intensity of the neuropathic state. This is predicated upon the assumption that impairment in vibratory sense is a function of impairment in the transmission of other sensory impulses in the involved peripheral nerve.

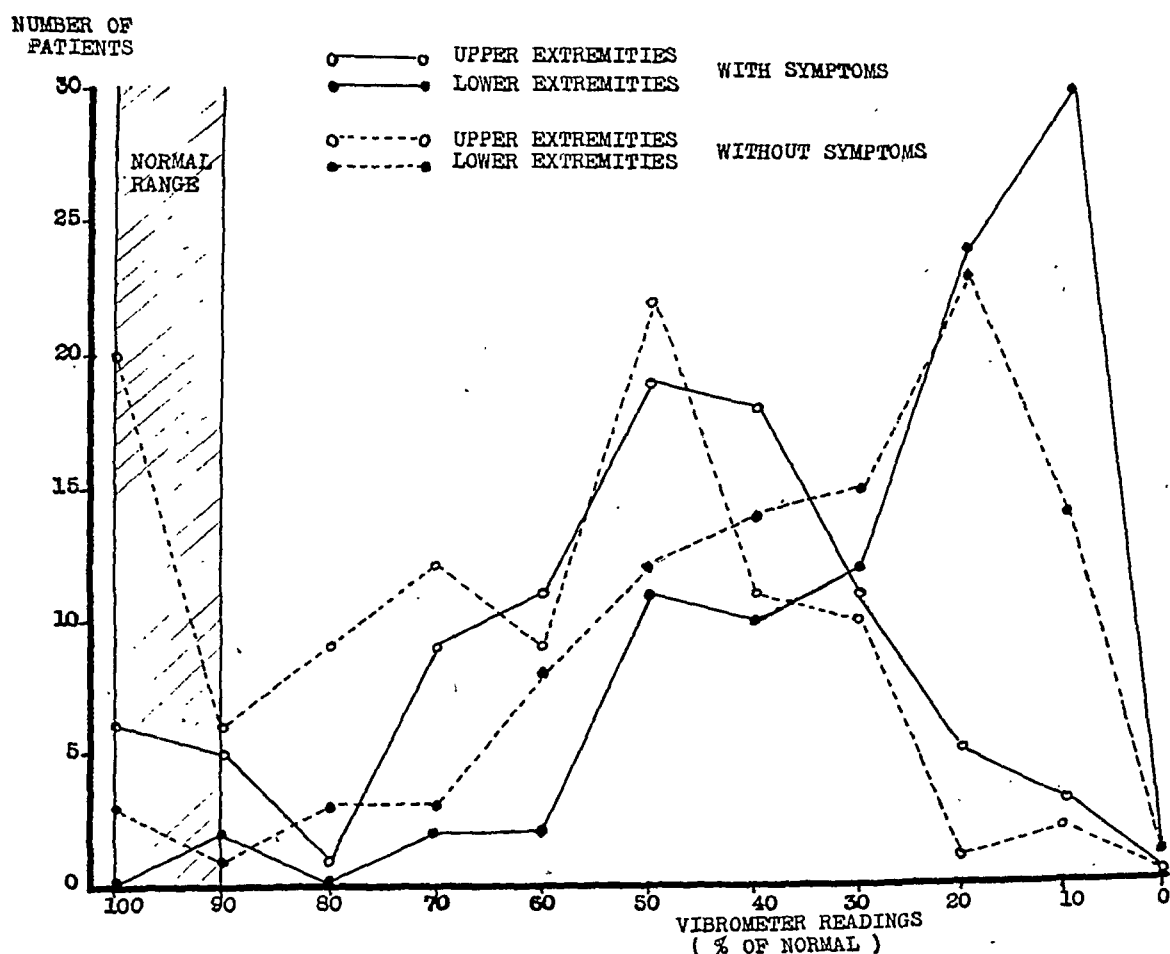


FIG. 1. Graph showing impairment in vibration sense in diabetes. Solid line represents patients with symptoms of peripheral neuritis. Broken line shows the patients without neuritic symptoms. Shaded area shows the normal zone. Shift in curve to right indicates an increasing number of patients showing more profound impairment in vibration sense. Note that the lower extremities are more severely involved in most of the cases than the upper extremities. Note also that the curve of patients without neuritic symptoms almost parallels the curve of cases with symptoms of neuritis.

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Vibratory Sense in Diabetes—Collens et al.

TABLE 1

No.	Age	Sex	Duration of Diabetes	Daily Insulin Dose—Units	Symptoms of Neuritis	Vibrometer Readings	
						Upper	Lower
1	13	M	2 yr.	53	None	100	70
2	16	M	3 yr.	60	None	60	30
3	18	F	9 mo.	78	None	80	60
4	13	M	3 yr.	57	None	70	60
5	19	M	6 yr.	95	None	90	70
6	12	M	7 mo.	65	None	100	100
7	11	M	1 mo.	15	None	100	90
8	10	M	2 mo.	25	None	100	40
9	23	M	9 yr.	130	None	100	100
10	17	M	11 yr.	35	None	100	60
11	8	F	2½ yr.	70	None	100	100
12	20	F	4 yr.	80	None	70	40
13	19	M	7 yr.	60	None	100	90
14	24	M	2 yr.	56	None	80	80
15	16	F	9 mo.	23	None	100	100
16	14	M	5 yr.	90	None	100	80
17	21	M	5 yr.	70	None	90	70
18	18	F	8 yr.	135	None	100	100
19	8	M	3 yr.	35	None	100	100
20	12	F	6 yr.	50	None	80	80
21	22	F	7 yr.	75	None	100	80
22	14	F	1½ yr.	42	None	100	100
23	23	M	7 yr.	90	None	90	70
24	7½	F	1½ yr.	60	None	100	100
25	12	M	6 yr.	80	None	100	100
26	13	M	1 yr.	55	None	100	100
27	16	F	4 yr.	65	None	70	50
28	21	M	4 yr.	72	None	100	50
29	8½	F	2 yr.	42	None	100	100
30	9	F	2½ yr.	128	None	100	100
31	14	M	9 yr.	72	None	100	60
32	16	M	3 yr.	100	None	100	80
33	17	F	2 yr.	100	None	100	100
34	17	M	5 yr.	35	None	100	50
35	6	F	1½ yr.	35	None	100	100
36	19	F	1 yr.	60	None	100	100
37	22	M	8 yr.	100	None	100	100
38	20	F	8 yr.	112	None	100	100
39	14	F	9½ yr.	74	None	100	100
40	22	M	3 yr.	55	None	100	80
41	17	M	4 yr.	144	None	100	100
42	7	M	3 yr.	50	None	100	100
43	16	M	11 yr.	90	None	100	100
44	25	F	9 yr.	36	None	80	50
45	20	M	16 yr.	112	None	100	80
46	24	F	22 yr.	68	None	100	100
47	15	M	2 yr.	53	None	100	100
48	19	F	9 yr.	112	None	100	100
49	22	F	5 yr.	60	None	100	70
50	23	M	3 yr.	95	None	100	70
51	17	F	6 yr.	85	None	100	100
52	13	F	2 yr.	52	None	100	100
53	13	M	2 yr.	60	None	100	100
54	20	F	2½ yr.	68	None	100	100
55	25	F	13 yr.	56	None	100	100
56	11	F	7 yr.	44	None	100	100
57	20	F	13 yr.	96	None	100	70
58	23	M	18 yr.	64	None	100	100

Recognizing that peripheral neuritis in diabetes assumes, generally, a stocking and glove distribution in the extremities without revealing any involvement according to somatic segmental levels, our plan of study consisted in testing the tips of the digits in the cases under observation. After observing that all the digits of the same limb gave approximately the same readings, it was decided, for purposes of simplicity, to record the readings on the tips of the index fingers of the upper extremities and of the large toes of the lower extremities.

This study is concerned with a determination of the threshold of vibratory sense in diabetics. Having once established the threshold of response with our instrument in 100 normal unselected individuals, we had a standard by means of which we could be guided in quantitating impairment in vibratory sense in diabetics. The first part of our study consisted in establishing these thresholds in 100 diabetics who presented classical neuropathic symptoms in the extremities consisting of one or more of the following: numbness, burning sensations, sticking pains, sensations of pins and needles, cramp-like pains, stiffness and formication. The second part of the study consisted in quantitating vibration sense in 100 diabetics who had no symptoms of neuritis. The accompanying figure (Fig. 1) is a graphic summary of these 200 cases. The ordinate is calibrated in terms of number of patients and is plotted against the vibrometer reading in the abscissa. It will be seen that in those with peripheral neuritis, there was not a single patient who revealed the existence of normal vibratory sense in the lower extremities and only two out of 100 showed normal readings in the upper extremities. It will also be observed that the majority of the cases had a much more profound impairment in vibratory sense in the lower than in the upper extremities.

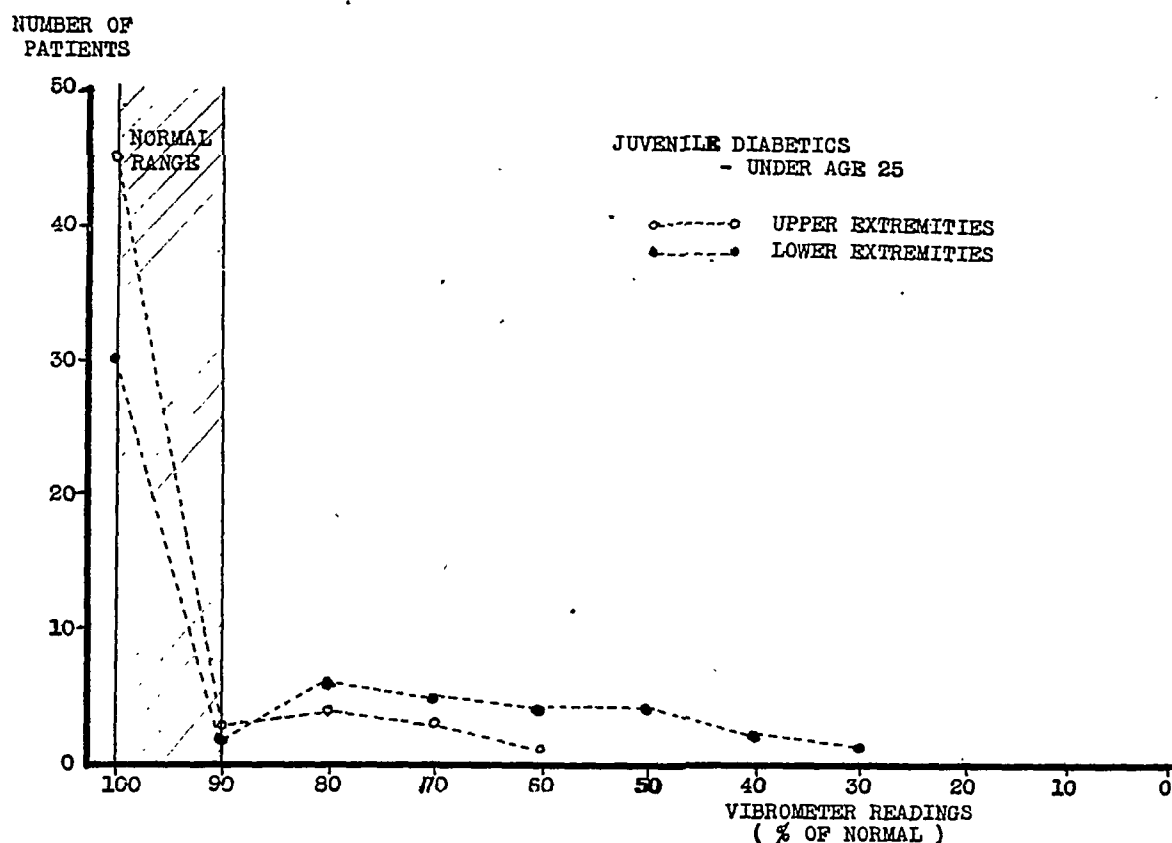


FIG. 2. Graphic summary of studies in vibration sense in fifty-eight young diabetics under twenty-five years of age. Note the small incidence of impaired vibratory sense and the mildness of the impairment.

What has proved to be most significant from this study is that diabetics who had no symptoms of neuritis whatever revealed an impairment in vibratory sense. It will be seen from the chart that only twenty-six out of 100 patients without symptoms gave normal readings for vibratory sense in the upper extremities and only four out of 100 had normal readings in the lower extremities. The remainder showed a specific impairment in vibratory sense. It is striking that the intensity of impairment in these cases is almost as great as in the diabetics with symptoms of neuritis.

It is apparent from this study that this method for testing vibratory sense has made it possible to detect the existence of a subclinical neuropathic state in diabetics who do not have symptoms of neuritis.

We then conducted a study of fifty-eight juvenile diabetics under the age of twenty-five. There are several pertinent observations in this group which, on analysis,

appear to be provocative and have upset some traditional concepts with regard to the rôle of the control of diabetes in relationship to the development of neuropathic states.

In Table I will be found a summary of these cases and in Figure 2 will be seen a graphic chart in which the number of cases is plotted against intensity of impairment in vibratory sense. The following conclusions can be deduced from these observations: First, there was not a single case who had symptoms of neuritis under the age of twenty-five; and second, the subclinical neuropathic state was found to exist in 14 per cent of the cases in the upper extremities and 43 per cent of the cases in the lower extremities. All the patients under the age of ten had entirely normal readings. There were six cases in this group. No patients had impairment in vibratory sense in the upper extremities of an intensity greater than 60 per cent of the normal and in the lower extremities greater than 30 per cent

of the normal. This would indicate that age plays a part in predetermining the development of neuropathy only past the age twenty-five.

What is most disturbing in the observations made in the juvenile group is that there does not appear to be any relation between the duration of the diabetes, the intensity of the diabetes, or the degree of control of the diabetes, and the intensity of impairment of vibratory sense. We can at this point cite the case of a female who developed her diabetes at two years of age. (Table I, Case 46.) She is now twenty-four years old and reveals normal vibratory sense readings at this date in spite of the fact that she is a severe diabetic and is satisfactorily maintained on a high carbohydrate diet with 68 units of insulin per day. On the other hand, this patient can be compared with another juvenile in whom diabetes was known to exist for only two months and vibratory sense studies revealed 40 per cent of normal in the lower extremities. (Table I, Case 8.) This child has proved to be a mild diabetic, is fully controlled and free from glycosuria, is thriving, and the total insulin requirement is 25 units per day.

We should like also to cite the severe case of a juvenile diabetic in whom the severity of the disease can be recognized by his insulin requirements which consist of 130 units per day. (Table I, Case 9.) His vibratory sense readings are entirely normal. It is interesting to mention in connection with this case that he has been diabetic for nine years and is seldom sugar-free.

Then there is also the case of a severe diabetic who has never been particularly cooperative and in whom persistent glyco-

suria and hyperglycemia have been characteristic features in spite of the fact that he has taken an average of 112 units of insulin per day. (Table I, Case 48.) He has had diabetes for nine years and his vibratory sense readings are normal. These observations have a tendency to upset our traditional concepts that adequate control of diabetes can protect the patient against the development of neuropathic states.

There is evidence that this phenomenon of impaired vibratory sense in the diabetic is reversible. This will appear in a paper on the treatment of peripheral neuropathies in the diabetic in the Proceedings of the American Diabetes Association.

CONCLUSIONS

1. Peripheral neuropathic states can exist in the diabetic in subclinical form and can be recognized by quantitative studies of vibratory sense.

2. In diabetics with peripheral neuritis, 90 per cent had impairment in vibratory sense in the upper extremities while 98 per cent had impairment in the lower extremities.

3. Impairment in vibratory sense occurs almost as frequently and almost as severely in diabetics without symptoms of neuritis as it does in those with symptoms.

4. No diabetic under the age of ten had any impairment in vibratory sense.

5. It appears from these studies that not only impaired vibratory sense but also symptoms of neuritis can develop in the diabetic regardless of the duration of the disease, the severity of the disease or the degree of control of the disease.

The Planning of a Camp for Diabetic Children

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IN the consideration of the problem of a summer camp for diabetic children, a problem which is growing and will increase as time goes on, it is believed that it is timely to bring forth the needs and the essential outlay of such a camp. It seemed unfortunate that all the advantages of a camp life had been denied to the diabetic child whose very life depended upon special medical care, restricted diet and the insulin syringe. Cognizant of this, I established a summer camp in 1929 near Cleveland for diabetic children.

The reasons were many. After the discovery of insulin, diabetic children were kept alive. They no longer presented the pitiful picture of slow starvation until death released them. But just keeping a child alive was no longer sufficient. A chance for his normal growth and development was essential. His life would have to parallel in all aspects that of normal children.

The diabetic child needs the advantage of a healthful vacation even more than does a normal child, for his daily routine is an onerous thing. The diabetic child needs the exercise which helps to metabolize his food intake. It has been discovered that exercise helps partly to replace the insulin up to a certain point, for insulin dosage can often be reduced considerably while a child is at camp.

More than other children, he is apt to be introspective and inclined to be a psychological problem. The very nature of his disease is the cause for this, as well as doting parents or unintelligent handling. By com-

munal living with many other children, diabetics like himself, he can realize for the first time that he is not alone with his problems. He has the advantage of seeing how others face theirs and solve them in healthy, normal ways.

The well controlled diabetic presents the most helpful and encouraging material with which to work. The majority of diabetic children have IQ's well in advance of normal children of the same age. By giving them the advantage of a normal outlet for their energies and initiative, their growth into responsible citizenship is assured.

Lastly, by providing a place of vacation for the diabetic child, the mother is relieved of her arduous task for a brief period in which she, too, can gain some rest and renewed strength to face the burden of the child's care when he returns home.

In the past eighteen years of Camp Ho Mita Koda's* existence, these ideas have proven beyond question its worth to the community and its invaluable service to the diabetic children. Because this camp has been the pioneer in this field, many questions have come to my desk concerning its nature and organization. In order to help others who might be interested in establishing like facilities for diabetic children, I herewith state my reasons for arriving at the present type of set-up, outlining briefly its physical aspect as well as its staff requirements.

* Ho Mita Koda is Sioux Indian and means "Welcome my friend."

CAMP SITE

The camp site is the first consideration. Should it be a separate camp, devoted just to the needs of diabetic children, or should such a camp be a small unit inserted into a general camp already existing?

There are advantages and disadvantages in both. A camp for diabetic children is a highly specialized camp, serving the needs of children as other camps do in addition to serving their medical needs. This latter presents no small item. If incorporated into a general camp, it has the advantage of a large group of children in its general program. The great disadvantage is that the diabetic child is constantly pointed out as such when little incidents occur, such as insulin reactions, the necessity of eating at a separate table, the need of laboratory work, etc. Thus the focus is on the diabetic child. This is automatically eliminated when such a child is in a camp solely for diabetics where all problems are alike. Such an association then in a general camp creates certain psychologic problems or reactions which are not desirable. It does not spare the child.

Another factor in a general camp is the maintenance of a corner in the kitchen to care for the diabetic diets. One will find in such a large kitchen more people, more confusion, more friction than when such a kitchen serves only the needs of diabetic children. It is a big load at best and should, therefore, not be made any heavier.

Thus, on the whole, I believe that it is much simpler, much more efficient, if the camp is devoted entirely to the needs of the diabetic.

THE PHYSICAL PLANT

The physical plant had to fill the following needs: (1) A central unit for all community activities; (2) sleeping quarters for campers; boys, girls; and the staff: men,

women; (3) toilet as well as bath facilities for the same.

THE CENTRAL PLANT

Main Hall. The Great Hall is the largest room in the main hall. Its focal point is a huge fireplace around which much of the program is built. The stage opens onto this room. Here children gather for talks, movies, plays and general discussions; here an occasional dance is held as well as radio programs. On rainy days, especially in the evenings, it is the chief center of activities.

Library. We realized that a library was needed in the camp. For lack of space we combined this room with the stage so that it serves a dual purpose. Here around an open fireplace is housed good literature for all age groups. The floor of the room is a foot and a half higher than in the main hall, with a wide opening to frame it as a stage when used for that purpose. It is a much needed and useful room in the planning of camp programs at night. Much stimulation can be induced for further individual initiative. Short sketches and skits, often spontaneous by the campers, are encouraged. It is stimulating as well as entertaining. The little ones try to imitate the older ones and to outdo them.

Dining Room. I have utilized a large screen porch on the main building, some 110 feet long, for dining purposes. This frees the main hall of unnecessary confusion and is much more enjoyable for it is almost out of doors. The children while eating, look out on the green lawn and trees, the fountain and the totem poles. It was essential of course that the porch be screened. While on the problem of screening, I might suggest one point: use copper screen throughout the camp. It is the greatest economy by far in the long run. All screen doors are reinforced with heavier mesh screening below where children's knees or feet have a way of opening them.

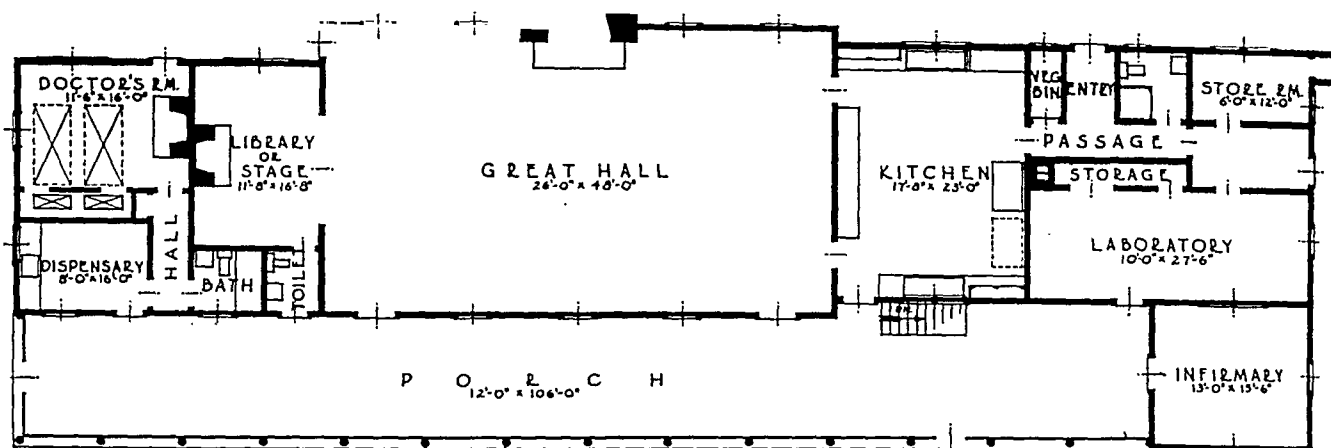


FIG. 1. Plan of main building for summer camp for diabetic children.

Kitchen. The kitchen in a diabetic camp is a very important and specialized unit. A graduate dietitian is in charge. She does all the planning, buying, measuring and supervising of all the details. Her task is easy in a general camp where the main issue is to provide good and tasty food and plenty of it. In a camp for diabetics, each individual child is on a planned diet which has to be calculated and weighed for each meal. The planning is done by the dietitian the night before in cooperation with the medical director. It is impossible in a camp of fifty to sixty children to prescribe fifty to sixty different diets, many of which would vary from each other by only a few Gm. It would be a useless waste of time. Thus diets can be grouped into about five or six routines in order to eliminate confusion. Each such diet, as a further check on its accuracy, is served on special colored plates; thus let us say, a 1,600 calorie diet is served on red plates, a 2,000 calorie diet on green plates, an 1,800 calorie diet on yellow plates, etc. This eliminates mistakes, for a child knows whether he is to get the yellow, the red or the green plates and if a wrong tray is offered him, he will immediately call attention to the fact.

A good cook under the supervision of the dietitian takes care of preparation of the food so that it is attractive, appetizing and of good nutritional value. The dietitian and her helpers, girls who are recruited

from among the older group of campers, serving a week or two at a time as a part of their training, measure the diet according to the outline planned by the dietitian. This assures rapid service and the food is palatable from the standpoint of its warmth.

Dish washing is done in a similar manner as in hotels. The dishes are rinsed in a unit of boiling water after preliminary washing and lifted from it in racks and allowed to air dry. The wiping of dishes is against a state law, and is thus eliminated in all camps.

Refrigeration is a large item. Food for seventy to ninety people, campers and staff, takes much space. Ice refrigeration for some foods is adequate. In addition an electric refrigerator is helpful, especially when a unit has to be opened at more frequent intervals.

A small cellar under the porch is a very useful item as much of the food can be taken care of in such a cool place, for the volume of vegetables, fruits, etc., is enormous.

Hot and cold running water is provided for the kitchen by a separate heating plant attached to the main building in which the kitchen is located. Also a large screened storage room and smaller bins are needed for vegetables, fruits and staples.

The disposition of the garbage may require a disposal unit unless one can arrange with some near-by farmer to haul

the garbage away daily. I have been fortunate to make such arrangements at my camp by agreeing to keep all paper and inedible objects separate. A small, screened unit for the garbage cans is essential a short distance from the main hall.

Infirmary. In an institution dealing with medical problems, the infirmary is a very necessary part of the set-up. Anything can happen in a camp. An infirmary meets the needs in all emergencies such as reactions, acidosis, isolation, etc. It is especially useful at night, for by removing a sick camper from the general sleeping quarters, the rest of the children are not disturbed. The infirmary and laboratory, too, are the headquarters for the night nurse. The infirmary is next to the laboratory where any needed test can be performed.

Laboratory. The laboratory is an essential part of the camp. Urine examinations, blood sugar estimations and other special tests, when indicated, are performed here. It also serves as the center of medical activity. For that reason it requires a fairly large room. The work is done by the staff consisting of a resident physician and nurses. In fact, regarding the urine examinations for instance, the question is often asked: Do the children do the urine analyses? The answer is "no." They come to camp not to be burdened with medical care of themselves. Furthermore, they do not come for instruction. That is the field of the family physician and it is not encroached upon. The camp is responsible for the medical care of the children while they are there; after that it turns them back to the family physician for his continued care and management.

We have a telephone with extensions in all vital sections of the camp.

Sleeping Quarters. Sleeping quarters are planned on the basis of the needs of this special group and on surroundings. We built units for eight to ten children. These

are open screened buildings, size 24 by 56 feet, giving ample room for cots and lockers and bedside tables. The units for girls are at some distance from those of the boys to insure privacy. In each unit children are grouped according to age. The roofs of all the buildings are insulated with celotex under the shingles which adds much to comfort during the hot summer. This point is quite essential to bear in mind.

Sleeping quarters for the staff were created in similar or in smaller units. A few small buildings accommodate husbands and wives. We have found that often young couples make good staff members. Sleeping quarters for the help, cook, assistant cook, handy man, etc., required separate small units. The quarters for the night nurse are at some distance from the general camp outlay to insure her undisturbed rest and sleep during the day.

One must bear in mind that these children require supervision at night. The night nurse must make rounds every half hour until midnight, then every hour during the rest of the night. She has to observe each sleeping cabin to see if all is well, checking to see if there are any insulin reactions during sleep. For that reason the buildings should not be too far apart. There are rainy nights. A camp on a rainy night with three to five reactions in separate buildings can present a terrific problem. Fortunately, since protamine zinc insulin came into use, this phase of the problem has been much reduced. It once was the major problem at the camp.

Toilet and Bath Facilities. It is cheaper to plan for all bathing and toilet facilities in one general building, the bathhouse, than in many separate buildings. Here again we had to provide for separate needs of campers, boys and girls; and staff, men and women. Our bathhouse is divided into four separate sections by complete partitions, each one to take care of the needs of each

of the four groups. Each room has its separate entrance from the outside and is broken down into space for toilets and another space for showers and wash stands. Hot showers, running hot and cold water and flush type toilets are provided in each of the four subdivisions. The heating unit is in the center part of the building. A septic tank provides for sewage disposal.

Water Supply. As camps are located far from the city, one has to provide for water supply. I solved this problem by drilling a well 132 feet deep, installing a deep well electric pump and a 5,000 gallon pressure storage tank underground. This has taken care of our needs adequately and efficiently.

Sewage Disposal. Sewage disposal had to be provided for the entire camp. As all the baths and toilets are housed in just two buildings, the bathhouse and the main hall, the problem was simplified. We built a large septic tank. The discharge from it, clear, unpolluted water, is lead underground to a convenient distance from the camp where it can empty into a running creek. In the kitchen, we did not forget the fat traps, as otherwise the sewage would be plugged up. Sanitary engineers helped here as state laws had to be complied with. At the close of camp each season, all water has to be drained to prevent the pipes from freezing.

Lighting. Electricity for all buildings is the safest means of lighting. It is needed also for the pump, the craft shop, etc. We were fortunate in having electricity wired into the camp. A Delco unit would have had to be installed if a utility line had not been available.

CRAFT SHOP

The craft shop is a separate building used for various activities. It is a place especially busy on rainy days. If properly conducted, it can do much for the children in teaching them to use their hands and their imagina-

tion. Here money is well spent in getting the best instructors available who can stimulate creative ability and latent initiative among the campers as well as teach them new and useful things to make.

PLAY AREA

Play space is important. The ideal acreage for a camp as set up by minimum standards of the American Camping Association is an acre per child or more. This allows for hiking, outdoor sports and activities of all types. We have provided a baseball diamond, archery court, tennis court, outdoor theatre, many camping sites and other special sites within the camping boundary.

Swimming Pool. If there is any single item of great importance during the camp season, it is swimming. It is a fine type of exercise and is refreshing. If such a camp is located on a lake or a good-sized stream, these can be utilized for this purpose. We were not so fortunate. Having no open body of water, we had to build a swimming pool. This required drilling a well for the additional water supply. To maintain the pool, all hygienic measures connected with swimming pools are carried out.

Outdoor Kitchen. Even though children are in a camp proper, they want their excursions, their hikes. Thus an outdoor kitchen at some distance from the main camp fulfills such a need. Here smaller children can have a picnic or overnight hike in order to learn primitive camping, self-reliance and improvisation as they will have to take their own insulin, cook and weigh out their own food, etc., under supervision. Yet they are within easy reach of the camp. We built our outdoor kitchen on the edge of the property. It has a roof supported by four huge chestnut uprights. The stove is of stone with ample cooking surface and a dutch oven. Other facilities are storage sheds and a pony barn.

THE STAFF

Some mention has already been made of staff members. Their duties are briefly outlined: The medical director directs the general medical care of the campers, makes any changes in insulin dosage that are indicated by blood sugar studies. He meets any medical emergencies that may arise from time to time. There is a resident physician to assist the medical director.

The nurses carry out the instructions of the physician. They give all the insulin, etc., exactly as in any hospital. The night nurse has her special duties of general supervision of the entire camp and is especially on the lookout for reactions or impending acidosis. The nurses do not wear uniforms. They wear the same type of sensible camp clothing as the counsellors for medical care and supervision, which though ever present, is kept in the background.

The dietitian has full charge of the diets, the buying of food and the serving of the meals. The cooks work under her supervision.

The counsellors have their special duties according to their assignment. Young counsellors of mature judgment are preferable as they can enter into the spirit of the camp and be a part of it. They should be of high caliber and of special training so that they will have something to offer to the children and command their respect.

A maintenance man is general utility man for the entire camp and should be responsible to the director.

CAMP PROGRAM

The camp program has developed along the most modern and progressive trends in group activity. Because of the very highly specialized medical regimen which must be adhered to for the child's safety, there is a skeleton schedule of waking, eating and sleeping, around which the rest of the pro-

gram revolves. Usually it develops as the days pass, according to the interests and inclination of the children, having no pre-camp pattern set for it. The counsellors who are highly trained, resourceful people, are capable of guiding or assisting the campers in their projects.

In this way the greatest amount of creativeness has been stimulated. The campers gain the highest degree of satisfaction from their experience because they have planned it themselves within their own groups, instead of following a predigested schedule cooked up before their arrival. Many graduate students have taken their group-work training at Ho Mita Koda.

FINANCES

To build such a camp involves a considerable investment. Just how much, will depend largely on the particular community and the cost of labor at the time. To start with it will represent an investment of at least \$50,000.00. Then there is the equipment, the upkeep and the depreciation to consider. The present worth of our camp with the equipment is about \$75,000.00. This does not include the upkeep, the depreciation and operational costs.

Let us consider the basic cost during operation as being \$5.00 per child per day. This is low when we consider the double function of the camp, the camping proper plus the full medical care comparable to hospital care. Such a camp thus has two staffs and consequently double expense as compared with ordinary camps.

If we figure on one dollar per day per person for food, we get the following figures:

A. Food—50 children	
	\$50.00 per day
23 adults	
	\$23.00 per day
Total \$73.00 × 30 is	
	\$2,190.00 per month
B. Staff Salaries—	
	\$2,405.00 per month
Total	
	\$4,595.00 per month

Income. The camp was incorporated on a non-profit basis to serve diabetic children according to their means. The top fee has been \$100.00 per month. Very few children have been able to pay this sum. Most children have paid on a sliding scale from \$100.00 to nothing. This means that supplementary sums have had to be raised to take

care of operating and maintenance costs. In the past the Cleveland Foundation, the F. P. Fenn Fund and the Rose Fund and private gifts have helped to provide the needed money.

It is an expensive proposition but worth the investment in the pleasure it provides and the concrete results it obtains.

Differential Diagnosis in Obscure Fever^{*}

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ABNORMALLY high body temperature has been the subject of study by the clinician from as far back as ancient times up to the present day. A brief résumé of the development of knowledge of the mechanism of the production of fever, a classification of those conditions commonly associated with fever and a plan of diagnostic attack will be presented.

That Hippocrates was aware of fever and its importance as a prognostic sign there can be no doubt. Fever was regarded as an expression by the body of a disturbance of its humors. Recovery resulted from the elimination of the "concocted" humors (crisis) or diminution of secretion or increase in excretion (lysis).

No outstanding contribution to the subject of fever was made after Hippocrates' time until the invention of the thermometer by Galileo between 1593 and 1597.⁷ Sanctorius, the father of the science of metabolism, began estimating the temperature of the human body with a thermometer in 1625. Although a clinical thermometer 3 inches (7.6 cm.) long was constructed by duVal in 1638, it was not accepted for general use. Between 1625 and 1745 Swammerdam, Haller and Martine kept the subject of thermometry alive from the viewpoint of physiology, but little or no clinical use was made of the instrument. De Haen in 1761 used thermometers in his clinic in Vienna.

In 1814, Davy clearly demonstrated the diurnal variation in body temperature. To Becquerel and Breschat (1835) is ascribed

the determination of 98.6°f. (37°c.) as the normal mean body temperature.⁹ In 1850, Traube challenged the Hippocratic "doctrine of the crises" and two years later published the first temperature curve to appear in the literature. He persuaded Wunderlich,¹⁷ an associate at Leipsig, to study clinical thermometry. In the next fifteen years he studied about 25,000 patients. In 1868 he published his classic monograph and established the fact that the course of certain diseases is revealed by the course of the body temperature.

Until 1867 when Allbutt invented a self-registering mercury thermometer, the thermometers in use were ungainly and inaccurate. Wunderlich's instrument was a foot long and had to be held in the axilla for twenty minutes. Small wonder that thermometry for clinical investigation was unpopular!

With the advent of a fairly accurate method of estimating body temperature, the study of metabolism begun by Sanctorius became a major undertaking. Outstanding among the men in this field has been DuBois⁹ who first became interested in the subject when he was a hospital orderly in the Spanish-American war carrying water to typhoid fever patients. In his monograph he has shown by calorimetric studies on normal human beings that production of heat by the body always equals the loss of heat.

On the basis of many studies in which human beings, normal and diseased, were subjects, DuBois concluded that the rise in

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temperature in fever does not depend on the level of production of heat or change in production but is due to an adjustment which keeps elimination of heat below production. This adjustment is made by the temperature regulating mechanism. Liebermeister¹³ has likened this to setting the regulating mechanisms at a higher level.

The thermoregulatory centers have been fairly well localized by Ranson.¹⁴ Centers controlling loss of heat are in the preoptic and supraoptic regions between the anterior commissure and optic chiasm. The center controlling production and conservation of heat is located in the caudal part of the lateral hypothalamus. It appears to be identical with the sympathetic centers. Best and Taylor⁴ stated: "From observations of patients with intracranial lesions involving the base of the brain, it seems most likely that in man the centers are situated as described by Ranson and his associates for animals. Lesions in the supraoptic region are associated, not uncommonly with hyperthermia; hypothermia, on the other hand, may accompany lesions involving the posterior part of the hypothalamus."

The thermoregulatory centers are influenced in three ways: (1) reflexly from the skin, (2) by the temperature of the blood flowing through them and (3) by toxic substances in the blood.

Hewlett¹² stated that, "in true fever, heat regulation is present but perverted." Hence lesions of the brain involving the thermoregulatory centers are not the cause of true fevers. Actually this question is of more than academic interest in differential diagnosis since, when a patient has a constant high temperature which will not respond to the usual measures for lowering of fever; the postulation that a lesion of the brain is present is warranted.

Before consideration of the diagnosis of the cause of fever, it may be well to review the causes of elevated temperature which

are physiologic, rather than pathologic. Temperature may rise to 104°F. for a short time after strenuous exertion. A convulsion in which hysteria is the etiologic factor may cause a rise in the temperature by the same mechanism. Digestion may cause a rise of from 0.5° to 1.0°F. A low grade fever is not unusual in the first trimester of pregnancy. The temperature gradually falls to normal after this period. A rise of several degrees may result from dehydration of body tissues. Patients of whom the physician must be wary are malingerers who may raise the thermometer reading by physical means.

CONDITIONS IN WHICH FEVER OCCURS

The following classification of the pathologic causes of fever is a useful tool in differential diagnosis and includes most of the possible causes. The classification includes: (1) Congenital conditions and birth injuries, (2) trauma, (3) mechanical factors, (4) toxic agents, (5) infectious diseases, (6) neoplastic diseases and (7) miscellaneous conditions.

Congenital Conditions and Birth Injuries. Concerning these little need be said since they are relatively unimportant causes of fever. Among them may be mentioned injury to the brain at birth, but according to Hewlett this would not be a true fever if control of temperature were lost. Reports appear in the literature from time to time of cases of so-called habitual hyperthermia.¹⁵ The patients have a temperature of 99° to 101°F. (37.2° to 38.3°C.). Another condition which might be included in the congenital group is the fever associated with so-called constitutional psychopathic inferiority.¹

Trauma. Thermal reactions which occur after cystoscopy, gastroscopy or bronchoscopy, so-called fracture fevers, and the slight rise in temperature following operations when no infection is found to account for the fever may be considered to be a result of trauma. Fever may be attributed to trauma in these cases when marked

leukocytosis is absent and the fever is short lived. However, secondary infection may supervene.

Fever which occurs after crushing injuries usually begins as simple fracture fever augmented by a toxic factor from the products of tissue destruction and maintained if the toxic element is severe or secondary infection sets in.

Mechanical Factors. Fever may result from factors which act directly on the centers that control temperature. For instance, following spinal tap the lowered pressure of the cerebrospinal fluid disturbs the thermoregulatory center. Other factors may act directly on the mechanism of dissipation of heat and fever will occur. In ichthyosis heat cannot be lost from the skin by the mechanism of vaporization, although some heat may be lost by radiation by the skin.³

Toxic Agents. Fever may occur in reactions to common drugs, such as alcohol, arsphenamine, iodides, bromides, belladonna, morphine and occasionally barbiturates. The diagnosis in many drug fevers is suggested by concomitant skin rash. By far the most important drug fever today is that due to sulfonamides. In a recent six months' period in a busy city hospital no less than one fever of obscure origin resolved each month when administration of sulfonamide compounds was discontinued.

Among other toxic reactions which cause fever may be mentioned all foreign protein reactions (including transfusion reaction) and reactions to pyrogens in rubber tubing.

In a broad sense fever associated with hyperthyroidism, heart failure and heat stroke fits into this group. Death of tissue in any part of the body may liberate toxic substances which cause fever. This occurs in pulmonary or myocardial infarction.

Infectious Diseases. In the diagnosis of infectious disease, not only the usual bacterial and parasitic infections of peacetime but also the tropical diseases which were

introduced in this country during and since the war must be differentiated. Since most bacterial disease can be diagnosed readily by isolation of the offending organism and most contagious diseases by the clinical picture, this relatively large group of fever producing diseases will not be considered in detail. Diagnosis of some infectious diseases will be considered in a later section.

In the absence of any positive history or physical findings the presence of fever should suggest the possibility of hidden infection. Perinephritic abscess may not cause marked pain and may elude diagnosis until a complication, such as rupture into the kidney, occurs. Usually, however, some tenderness and spasm of the loin is present and leukocytes number from 20,000 to 30,000 per c. mm. of blood. The abscess is usually metastatic and the primary lesion, such as a small furuncle on the skin, may be insignificant.

Another difficult diagnosis is hepatic abscess. It may occur many years after an amebic infection of the colon or it may occur only a few days after a pyogenic infection such as acute cholecystitis or acute appendicitis. Confirmatory findings in the pyogenic type are pain in the region, enlargement of the liver and septic type of fever.

Although histoplasmosis is a rare disease, it would be diagnosed more frequently if it were considered as a possibility in all diseases characterized by chronicity, fever, emaciation, leukopenia and splenomegaly.

Neoplastic Diseases. Just what mechanism produces fever associated with neoplasm is open to conjecture. Undoubtedly, toxic-degenerative processes play a part but frequently no evidence of necrosis is seen in microscopic sections of the tumor. From the diagnostic point of view, the mechanism is not so important as the fact that the fever does occur. Neoplasm should be considered in all cases of fever of unknown cause but

particularly in cases in which adequate diagnostic procedures and therapeutic trials have not revealed infection. Fever may be the sole symptom for many weeks in the early part of the illness of a patient who has bronchogenic carcinoma.

In a study of 238 cases of carcinoma in various sites Briggs⁵ found that in more than a third fever was noted in some phase of the illness. He stated, however, that its occurrence as a pronounced feature of the disease is an unusual finding. He found that fever was present in 60 per cent of cases of carcinoma involving the lung and pleura. Another point to bear in mind is that a lung abscess occasionally may result from the breakdown of a neoplastic process.

Miscellaneous Conditions. At least 95 per cent of the cases in which the temperature is abnormally elevated can be classified in the foregoing six main groups. In the seventh (5 per cent of cases) fall the miscellaneous conditions in which the cause of fever is obscure. In some of these conditions the cause of fever may be toxicity, infection or neoplastic diseases associated with destruction of tissue.

Among the more important of the miscellaneous conditions are: periarteritis nodosa (fever in 80 per cent of cases),¹¹ verrucous non-bacterial endocarditis, disseminated lupus erythematosus, blood dyscrasias such as leukemia, diabetic acidosis, bleeding duodenal ulcer (fever in 80 per cent of cases), cirrhosis of the liver (in 50 per cent of cases),¹⁰ psychogenic fever and fever of unknown etiology.

Dill and Isenhour⁸ in their study of the cause of fever in cases of bleeding peptic ulcer made control studies of normal subjects. When they introduced blood into the gastrointestinal tract no fever occurred.

DIAGNOSIS

The diagnosis of an unexplained fever is one of the most difficult problems in

medicine and for this very reason one of the most interesting and satisfying to the clinician when a correct diagnosis is attained. Truly, the study of fever is the study of medicine because the cause of fever may be related to any organ or any tissue in the body.

History. As in all diseases, this is probably the most important when a clear-cut story can be obtained. Geographic location, contact with either human beings or animals that may have an infectious disease, and periodicity of fever should always be considered.

Because the geographic locations of endemic areas of disease should always be kept in mind in eliciting a history the clinician will do well, in these times, to provide himself with maps showing the endemic areas of such diseases as malaria, typhus and histoplasmosis. It is also important to ask the patient about his contact with persons who have contagious disease. Contagious diseases, particularly those in which skin rash is not present, should be considered in the differential diagnosis.

Frequently the type of temperature curve shown by observation of the patient for several days or weeks will give a hint as to the diagnosis in malaria, Hodgkin's disease (Pel-Ebstein fever) and the response of rheumatic fever to salicylates. The monograph by Ask-Upmark on periodic fever is well worth reading.²

If a veteran who has returned recently from New Guinea complains of chills and fever which occur every other day, malaria certainly would be considered as the first possibility. Brucellosis would be the first consideration when the patient is a farmer or even a city dweller whose fever began shortly after he drank unpasteurized milk. If a patient relates that he has dressed wild rabbits, the possibility of tularemia must be considered.

Probably the most important factor in establishing toxicity as a cause of fever is the history. Frequently when a patient is asked if he has taken any medicine or drugs lately, the answer will be "No" but on further questioning he may say that he has been taking a tonic which frequently proves to be "Doctor So and So's nerve elixir," which contains bromides. When a patient who is not being given any medication has a fever in the immediate postoperative period, the internist will do well to bear in mind the routine at operation of placing 5 Gm. of one of the sulfonamide drugs in the peritoneal cavity or surgical wound. Fever has resulted from reaction to just this relatively small amount of the drug.

In interpreting the history the negative side must also be given consideration. Drug fever may occur although the patient has not ingested the drug by mouth. A negative history of alcoholism does not rule out cirrhosis of the liver.

Certain patients may interfere with the taking of a good history involuntarily by stressing the importance of fever when actually it causes no distress.

Physical Examination. Special attention should be given to the search for rashes, incipient jaundice, enlarged lymph nodes, nodules on vessels or in muscles, hard prostate gland, tender regions in bone, small draining sinus and pathologic fractures. In rare instances, barbiturates will cause a rash and fever almost indistinguishable from scarlet fever. In these cases it is well to isolate the patient even though the diagnosis of drug fever is the more likely one.

Laboratory Studies. Serologic studies, repeated cultures, determination of the sedimentation rate, and smear and culture of the blood often will yield important diagnostic information. In a case in which the presence of histoplasmosis is suspected, smears of the peripheral blood will at times show parasitized mononuclear cells. Sternal

puncture will reveal a greater number of positive smears. Cultures which are thought to contain *Histoplasma capsulatum* should be kept a month before being declared negative.

Urinalysis and culture of the urine should be carried out. If, for any reason, the presence of ova or parasites in the gastrointestinal tract is suspected, the feces should be examined. Erythrocyte, leukocyte and differential counts should be made. It should be borne in mind that absence of eosinophilia rules out neither periarteritis nodosa nor trichinosis. Blood agglutination tests for typhoid, paratyphoid, tularemia and brucellosis should be made when the presence of one of these diseases is suspected. The diagnosis of rickettsial diseases can be made or ruled out when the Weil-Felix complement fixation is carried out. All the rickettsial diseases are important and a positive Weil-Felix reaction should be looked for. To differentiate Rocky Mountain spotted fever from other rickettsial diseases a complement fixation test should be performed. Results become positive during the second week of the disease.

Examination of gastric washings and sputum are particularly useful in the diagnosis of tuberculosis. Neoplasms of bone and lesions due to metastasis from prostatic carcinoma may be diagnosed from the results of determination of the acid and alkaline phosphatase in the blood. Determination of the basal metabolic rate may be a useful procedure. In fevers associated with hyperthyroidism and infection the basal metabolic rate is increased. It is normal in habitual hyperthermia. It may be normal in hyperthermia due to a brain lesion.¹⁵

Several pitfalls common to the interpretation of the results of all diagnostic procedures must be borne in mind. A positive result of the agglutination or skin test for *Brucella* is not necessarily diagnostic of brucellosis. Also if the sedimentation rate

is high and results of the agglutination test are positive some condition other than brucellosis is probably present for in brucellosis the sedimentation rate is relatively low to normal.⁶ Diagnosis of brucellosis is best made by positive blood culture, for the fact that the patient has been in contact with infected animals does not necessarily mean that he has become infected.

In the absence of positive findings on examination of the sputum or gastric washings and on subsequent inoculation of guinea pigs the diagnosis of pulmonary tuberculosis is best made by means of serial roentgenograms. Negative results of examination of gastric washings on several successive days merely mean that the patient is probably not a menace to his family. They do not rule out the diagnosis of tuberculosis.

Roentgenologic Examination. Roentgenograms of the pelvis, thorax and long bones may reveal evidence of the pathologic condition which is causing the fever. Evidence of metastasis may be found in long bones and presence of stones in the pancreatic region may be noted. Roentgenologic examination of the gastrointestinal tract may be necessary to rule out the presence of a polypoid type of neoplasm which is asymptomatic until it has metastasized.

Laparotomy. Walters and Snell¹⁶ have reported a case of cholecystic disease in which intermittent fever was the only symptom. There was no jaundice, no pain and no roentgenologic evidence of stones. Yet, on laparotomy stones were found in both the cystic and the common ducts. Mention is made of this to show that sometimes laparotomy serves as a diagnostic procedure in unexplained fever. Whether it is warranted or not is a moot question.

Therapeutic Tests. Several therapeutic tests are helpful in establishing the type of fever. Fevers due to infections can be treated successfully by administration of anti-

pyretics but the temperature rarely falls when narcotics are given. The elevated temperature in habitual hyperthermia and the "neurosis" type of fever is not reduced by administration of antipyretics but is reduced when morphine or some other narcotic is given.

Antibiotic and chemotherapeutic agents can eliminate fever due to infection by terminating the infection. Administration of these agents is a standard procedure in the diagnosis of unexplained fever after drug fever has been ruled out. These drugs rarely reduce the fever unless some infection has been overlooked in the other diagnostic procedures.

Another confusing point in the toxic picture when a reaction due to the sulfonamide drugs occurs in older people is the association of cerebral symptoms which sometimes leads to a mistaken diagnosis of cerebral vascular accident. The quick recovery of these patients when they drink a glass of water every hour and are given a little sodium bicarbonate rules out the possibility of cerebral infarction. Also the blood pressure tends to stay at a fixed level in toxic reactions. A therapeutic trial of emetine may confirm the presumptive diagnosis of amebic abscess of the liver even when results of examination of the stools are negative.

Treatment with roentgen rays may be given when a presumptive diagnosis of lymphoblastoma has been made. This sometimes gives surprisingly gratifying results.

Microscopic Examination. Biopsy of a node, vessel or nodule in skin or muscle may be the only positive means of diagnosing lymphoblastoma, periarteritis nodosa or trichinosis. In a small number of cases a diagnosis cannot be made even at necropsy.

SUMMARY

True fever is due to a disturbance of the thermoregulatory centers. Fever results

when these centers keep elimination of heat below the level of production.

The usual causes of fever can be grouped under the following headings: congenital conditions and birth injuries, trauma, mechanical factors, toxic agents, infectious diseases and neoplastic diseases. This group accounts for about 95 per cent of all fevers. A few conditions which do not fit under these headings but which always should be considered in the differential diagnosis are: periarteritis nodosa, verrucous endocarditis, disseminated lupus erythematosus, blood dyscrasias, diabetic acidosis and cirrhosis of the liver.

A plan of diagnostic attack has been presented, the main features of which are: (1) critical evaluation of the history, (2) critical evaluation of the laboratory findings and (3) emphasis on alertness for evidence of malignant disease.

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Treatment of Severe Functional Headaches

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THE pathogenesis of headaches has been the subject of extensive and fruitful investigation during the past decade. A number of etiological factors have been uncovered and many of the older beliefs have been subjected to critical appraisal. For instance, the experimental studies of Eckardt et al.⁴ have shown that myopia (artificially produced) will not cause headache, contrary to common belief. However, astigmatism and hypermetropia will do so. Williams¹² recently classified sinus headaches as an allergic phenomenon involving the cranial muscles. Horton et al.⁸ have described a peculiar syndrome of headache associated with sweating, lachrymation and other phenomena which can be precipitated or reproduced by injections of histamine; in these cases the vasodilator action of histamine is said to be the causative factor. In a recent discussion of the pathogenesis of headaches Wolfe¹³ outlined the chief mechanisms as follows: (1) spasm of the cranial or cervical muscles; (2) compression, traction or inflammation of the sensory cranial or cervical nerves; (3) traction on or displacement of the large veins and adjacent dura. (4) distention, traction and dilatation of the intracranial and/or extracranial arteries. In keeping with this last mechanism are the findings of Atkinson² who believes that the scotomas of migraine are vasoconstrictor phenomena while the headache itself is a secondary vasodilator reaction.

The manifest importance of vasomotor disturbances as a factor in the pathogenesis

of functional headaches has led to the investigation of drugs which alter the cerebral circulation. The nicotinic acid group has been studied intensively both experimentally and clinically.

The free nicotinate radical is directly responsible for the vasodilator activity of sodium nicotinate, nicotinic acid, the other ionizable salts and even quinine nicotinate. The amide (nicotinamide) and the diethylamide (coramine) have no vasodilator activity.³ The vascular action of the nicotinate radical is opposed by adrenalin³ and is not synergized by prostigmin,⁹ showing that its action is directly on the blood vessels and not via the autonomic nervous system.

Moore¹⁰ studied the effect of niacin on the pial vessels by direct visualization and was able to photograph the vasodilatation it produced. Aring et al.¹ measured the cerebral blood flow and found that increased circulation persisted for as long as an hour after intravenous injection of 100 mg. of niacin.

Limited reports of the clinical value of these vasodilators have appeared in the literature from time to time. Rogers¹¹ mentioned one case of migraine in which the attacks could be aborted by 100 mg. of nicotinic acid in oral doses; Enrique⁵ described the dramatic relief of a single acute attack of migraine by 100 mg. intravenous dose of nicotinic acid. Atkinson² has reported good results in the prolonged treatment of "histamine-negative" migraines with oral and parenteral niacin. Williams¹² administered courses of oral and intra-

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muscular niacin for sinus headaches with relief in 69 per cent of seventy-eight patients. Zeligs¹⁴ recently reported twenty-five cases of malarial headaches, resistant to all the usual drugs such as ergotamine tartrate, analgesics, etc. One hundred mg. doses of niacin provided complete relief in 40 per cent, moderate relief⁶ in 32 per cent.

In a recent paper, one of us (J. W. G.) reported the results of treatment of 100 consecutive cases of severe headache, regardless of etiology, with sodium nicotinate intravenously. Seventy-five per cent were completely relieved by a single injection and 9 per cent had only minimal recurrence within 24 hours. Since the publication of these data we have treated a considerable number of patients with migraine, and severe idiopathic headache, and a few more patients with cephalalgia following lumbar puncture. The results have continued to be as favorable as previously reported. This later material, however, could not be followed as closely nor investigated as carefully as the hundred original cases and hence does not lend itself for statistical comparison.

There is another factor in the pathogenesis of migraine and related headaches which is of the greatest importance. It has been shown⁷ that there often is an easily demonstrable disturbance of tissue hydration (i.e., salt and water metabolism) in patients suffering from such headaches. It is a generally recognized fact that migraine occurs more commonly during the premenstrual period and during menopause, when disturbances of salt and water metabolism are nearly always present. In a series of 150 cases of migraine and migraine-like headaches which were submitted to electrolyte balance studies, it was found that 90 per cent of the patients showed definite water retention and 84 per cent showed retention of sodium chloride under the conditions of a salt tolerance study. Cor-

rection of the metabolic disturbance resulted in complete cures in 44 per cent, great improvement (reduction of headaches to mild, occasional attacks) in an additional 25 per cent, improvement in 21 per cent and failure in 10 per cent.

THERAPEUTIC APPLICATIONS

Appreciation of the importance of these two factors (i.e., vasomotor disturbances and changes in tissue hydration) has led to many innovations in the methods of headache therapy and to increased efficacy of treatment.

Intravenous sodium nicotinate may prove to be a valuable therapeutic tool if used with discretion. Indications for its use are as follows:

1. It must always be kept in mind that such vasodilator therapy is purely symptomatic, and as far as we know, will not alter the severity or frequency of subsequent headaches in patients suffering from migraine or other recurrent forms of functional cephalalgia.

2. Intravenous sodium nicotinate should be used only for severe headaches. A patient with a mild headache will not be thankful for the manifest discomfort of the flush and thermesthesia which an intravenous dose of 100 mg. will produce.

3. It appears that such vasodilator therapy is particularly effective in the immediate treatment of migraine and migraine-like headaches, as well as of those following lumbar puncture, air encephalography or similar procedures. At the present time we believe that sodium nicotinate is to be preferred to the usual drugs employed in these conditions. There is no other way short of the use of powerful narcotics to alleviate the headaches following a lumbar puncture. The use of ergot derivatives such as ergotamine tartrate and ergonovine is subject to certain disadvantages. A relatively large proportion of patients do not tolerate these

drugs well; the gastric symptoms may be most distressing. The danger of ergot poisoning, though remote, must always be kept in mind when dealing with patients who suffer chronically with migraine. By way of contrast, sodium nicotinate is a non-toxic drug: 1,000 mg. per kilo body weight may be given to dogs for prolonged periods without any ill effects. In man, slight nausea may be felt during the flush; very rarely actual vomiting occurs. We have seen only a single instance of this reaction.

Contraindications to the use of sodium nicotinate are few. As already pointed out, it is too potent an agent to be used in mild headaches. The other feature which must be considered is that of dosage. The 100 mg. intravenous dose which we have used was selected arbitrarily as being large enough to produce vasodilatation in almost every instance. It may be wise, as with every other drug, to suit the dose to the patient, those with evidence of vasomotor instability (such as blushing on slight psychic stimulus, etc.) requiring smaller doses.

We have not found oral therapy to be of value.

The second aspect of the therapeutic approach aims at correcting the underlying salt and water imbalance if present. Clearly, such therapy is not merely symptomatic but is directed at an underlying etiological factor. Correction of this factor may bring about permanent alleviation of the recurrent headaches. The presence of salt and water retention may be demonstrated quite simply by the salt tolerance test. This is carried out as follows:

The patient is instructed to eat and drink exactly the same things, in identical quantity, for two consecutive days. Separate twenty-four-hour urine specimens are collected on these days. At 10 A.M. of the second (test) day the patient is given 10 Gm. of enteric-coated salt tablets and 250 cc. of water to drink. Total urinary chloride ex-

cretion on both days is determined by the usual laboratory method. If the patient does not excrete at least 7 Gm. more salt on the second day, and if he does not put out 200 cc. more urine on the second than on the first day, definite salt and water retention is present.

Salt and water retention can be demonstrated, appropriate therapy will give excellent results in at least 70 per cent of cases. Therapy is aimed at reduction of tissue salt and water as well as at decrease in vasomotor instability. The means by which this may be done are as follows:

1. High-protein, low-carbohydrate diet. High protein diets are definitely diuretic, partly because of their purine content and partly because of the resulting stimulation of certain endocrine glands. Carbohydrates, on the other hand, are antidiuretic, possibly by stimulating increased insulin production. Underweight patients should receive adequate supplements of fat to prevent any undesirable loss of weight.

2. Limitation of fluids to 1,500 cc. per day.

3. Reduction of dietary salt intake to an absolute minimum.

4. Diuresis for simultaneous removal of water and tissue salt. This is accomplished by alternate weekly courses of ammonium chloride 0.5 Gm., three times a day, and potassium acetate or gluconate 0.5 Gm., three times daily. In severe cases, injection of small doses of posterior pituitary extract may be valuable, for the transient antidiuretic effect of this hormone is followed shortly by an increased excretion of sodium chloride.

5. A combination of atropine (0.2 to 0.3 mg.) with phenobarbital (15 mg.) three times a day should be used to combat vasomotor instability.

A therapeutic response to this regimen, as evidenced by a diminution in the frequency and severity of the headaches, should be-

come apparent within about two weeks. During this time attacks may be treated with sodium nicotinate as outlined above. The dehydration routine should be maintained rigidly for at least two months, after which treatment may gradually be reduced and eventually withdrawn. However, the basic features of this antiretentional regimen, namely, fluid and salt restriction as well as high-protein, low-carbohydrate diet, should be continued by the patient. Attention to these dietary limitations should not prove overburdensome to the patient, especially when it means freedom from incapacitating headaches.

There is a type of migraine patient who develops attacks premenstrually, yet contrary to the findings in the majority of these cases, performance of the salt tolerance test shows no retention of salt. As a matter of fact, the sodium chloride excretion of these patients on an unlimited diet is usually quite high, well above 10 Gm. per twenty-four hours. These patients, who are underweight as a rule, do not respond to the treatment outlined above, quite in accord with the theory which does not lead us to expect beneficial results from further increased losses of sodium chloride. Hence we tried a different approach in a small group of such cases: Adrenal cortical extract was administered both orally and parenterally a few days before the expected attack. This treatment successfully prevented the onset of migraine headaches in all twelve patients in which it was tried.

The number of observations so far is much too small to draw conclusions, nor do the data available at present explain the mechanism by which the cortical hormone interferes with the development of a migrainous state. The well established anti-histamine effects of the cortical hormone deserve consideration. One could also propose, as another explanation, that the cortical hormone accomplishes results by

correcting disturbances of electrolyte metabolism. In the meantime, until further data become available to establish a sound basis for hormonal therapy, the use of this experimental approach seems justified in migraine cases of the premenstrual type in which salt retention is not demonstrable by the salt tolerance test.

The indications for each of these methods of therapy are quite clear. Vasodilator therapy is indicated for the isolated episode of severe cephalalgia, especially following lumbar puncture or similar procedures. It is also used to alleviate migrainous attacks while the slower acting therapy of antiretentional regime is brought into play. The intelligent combination of these two procedures should provide both symptomatic relief and permanent therapeutic effect in most cases of migraine.

CONCLUSIONS

1. The mechanisms involved in the production of headaches are reviewed briefly and the importance of vasomotor changes and disturbances in tissue hydration are discussed.
2. Methods of therapy based on the correction of these two factors are outlined on the basis of two series of 100 and 150 patients, respectively.

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Seminar on Antibiotics

Penicillin in the Treatment of Syphilis*

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SYPHILIS is a disease of such exquisite and capricious chronicity that an evaluation of the ultimate results of any form of therapy requires a prolonged period of post-treatment observation. Penicillin has been used in the treatment of syphilis for but a few years. Hence, discussions of its use in this disease necessarily must be tempered, being subject to revision perhaps even in the immediate future.

Factual data on penicillin in syphilotherapy have accumulated with meteoric rapidity. This has been possible only because it has been studied on a cooperative and integrated nationwide basis. In September 1943, only three months after Mahoney's original report¹ that *T. pallidum* is susceptible to the action of penicillin, a cooperative study of the effect of penicillin in the treatment of syphilis was organized under the auspices of the Committee on Medical Research. Participating in this study are forty-one clinics and eight laboratories of experimental syphilis. As a result of their collective efforts, an enormous amount of information has been compiled. In the first three years approximately 35,000 patients were treated, and the results (for early syphilis) reported to a central statistical unit. With these significant data available, preliminary evaluations of the early results of penicillin therapy are possible.

Even the most skeptical observer no longer denies that penicillin is a valuable

adjunct to syphilotherapy, nor that it is, in some respects, superior to any previous form of treatment. That it has serious limitations is recognized by its most ardent protagonists.

The *ideal treatment* of syphilis would be that which is: (1) completely and uniformly effective, (2) entirely devoid of toxicity, and (3) readily administered with a minimum of inconvenience to the patient and to his physician.

Penicillin is effective, but not uniformly nor always completely so. It is, in marked contrast to metal chemotherapy, non-toxic, approaching the ideal in this respect. It is relatively easy to administer, and therapeutically effective amounts can be given in a comparatively brief period of time.

The principal *advantages* of penicillin in the treatment of syphilis are: (1) its lack of toxicity, and (2) the fact that the therapeutic schedule need not be inordinately prolonged. Consequently, the full course of treatment is almost invariably completed. This is not the case with any form of arsenotherapy in which toxic reactions increase in frequency the more the time interval is compressed, and in which case-holding becomes increasingly difficult as the duration of therapy is prolonged.

Penicillin is a relatively innocuous substance. The untoward reactions thus far reported to have followed its use have been confined almost exclusively to allergic manifestations in the skin.² These reactions

* From the Venereal Disease Division of the Medical Clinic, the Johns Hopkins Hospital, and the United States Public Health Service and Johns Hopkins University Venereal Disease Research and Post-Graduate Training Center.

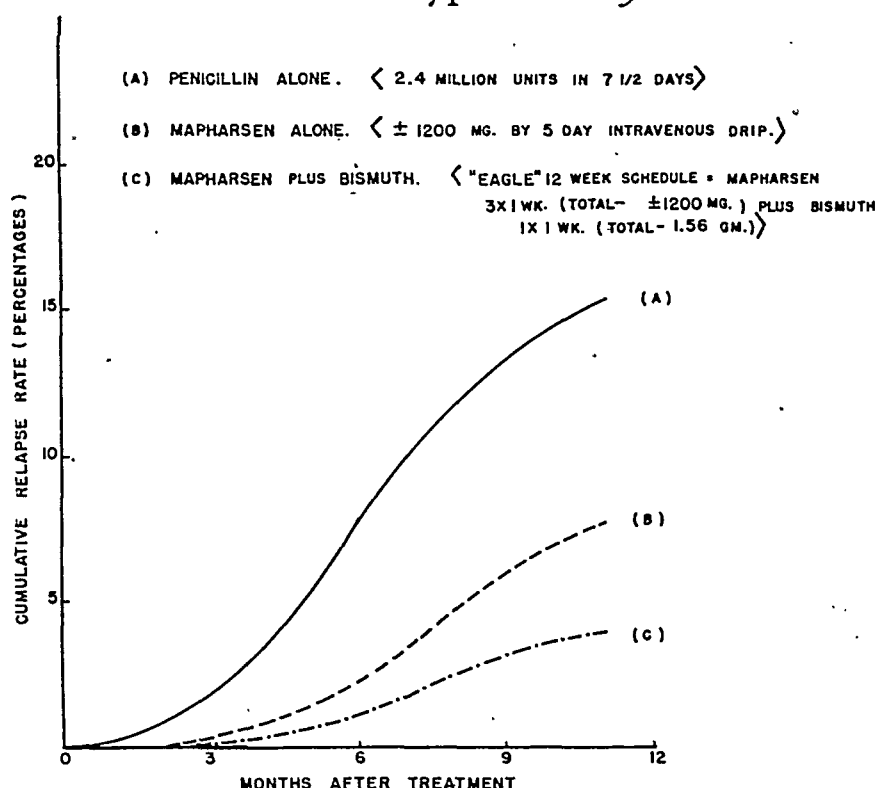


FIG. 1. Cumulative percentage relapse rates with treatment schedules utilizing; (A) penicillin alone (2.4 million units); (B) mapharsen alone (1,200 mg.); and (C) mapharsen (1,200 mg.) plus bismuth (1.56 Gm.). USPHS data, smoothed curves.

may occur shortly after the institution of therapy as a result of a pre-existing hypersensitivity, or late in the course of treatment because of developing dermal sensitization. Delayed "serum-sickness-like" reactions occur, but are extremely rare.³ The incidence of serious toxic reactions is negligible, for in less than one patient in several thousand⁴ treated for early syphilis with penicillin do untoward reactions necessitate interruption of the course of therapy. Herxheimer reactions are frequent, especially in early syphilis, in which approximately 75 per cent of patients treated develop fever with transitory intensification of the early tissue reaction. Milian's syndrome ("Erythema of the Ninth Day") has not been reported.

The principal *disadvantages* of penicillin therapy (at least with any schedule of administration the results of which are presently available) are: (1) the probable essentiality of hospitalization, when the drug is given in aqueous solution, and (2) the significant number of treatment failures

(relapse and seroresistance in early syphilis, sub-maximal improvement in certain forms of late syphilis).

The necessity for hospitalization of patients receiving penicillin as therapy for syphilis significantly reduces its general utility, for the number of hospital beds available for this purpose is limited. The United States Public Health Service has done much to obviate this difficulty through its in-patient Rapid Treatment Center program. Nevertheless, there are many to whom the necessary hospital facilities are denied.

To be feasible for ambulatory syphilis patients in the clinic and in the physician's office, a modified penicillin with prolonged activity is required. Many attempts have been made to extend the duration of penicillin action, either by delaying its absorption or by blocking its renal excretion. By far the most satisfactory modification presently available is the suspension of penicillin in peanut oil and beeswax devised by

Romansky and Rittman.⁵ With a preparation containing 300,000 units of calcium penicillin with 4.8 per cent beeswax contained in 1 cc. of peanut oil, detectable blood levels can be maintained for approximately twenty-four hours following a single injection in 75 per cent of the patients treated.⁶

Penicillin in oil and beeswax ("POB") has been used in the treatment of syphilis. Preliminary reports^{7,8} suggest that the results may be sufficiently satisfactory to warrant more widespread application. Treatment schedules utilizing POB alone and in combination with mapharsen or bismuth currently are being evaluated by the clinics cooperating in the nationwide syphilis study.

With any schedule of penicillin administration thus far studied, the incidence of infectious relapse and of seroresistance (in early syphilis) has been significantly higher than those with "adequate" metal chemotherapy. For example, the incidence of infectious relapse following 2.4 million units of penicillin in seven and one-half days has been approximately *five times* that with a twelve weeks' semi-intensive course of mapharsen and bismuth. (Fig. 1.)

Comparative ineffectiveness of penicillin is less than appears from this figure. Present information indicates 2.4 million units is a small total dosage and seven and one half days a brief period for administration. The data are for commercial penicillin; the therapeutic value of some is now known⁹ to have been low because of its high content of penicillin K. This fraction, although active *in vitro* against the test strain of *Staphylococcus* used to determine its potency in terms of Oxford units, is destroyed in the body to a significant degree,¹⁰ and is known to be decidedly inferior to other penicillin fractions in the treatment of experimental rabbit syphilis.¹¹ Also, the comparison of relapse rates following penicillin treatment

with those of metal chemotherapy must be made with the knowledge that the recorded percentage of relapse refers only to those who actually completed the full schedule of therapy. Not indicated in Figure 1 is the fact that a sizeable proportion of patients who undertake ambulatory arsenobismuth therapy become delinquent, and fail to receive the full course of treatment.

A more satisfactory comparison between penicillin and metal chemotherapy in the treatment of (early) syphilis may be made by taking into account the three attributes of the "ideal" therapeutic agent: effectiveness, lack of toxicity and convenience of administration. (Table I.)

TABLE I
A COMPARISON OF PENICILLIN WITH METAL CHEMOTHERAPY
IN EARLY SYPHILIS, IN RESPECT TO EFFECTIVENESS,
TOXICITY AND CONVENIENCE TO THE PATIENT

	"Effectiveness" (as relapse rates after 11 months) Per Cent	"Toxicity" (as deaths due to treatment)	"Convenience" (as per cent. of patients completing full course of therapy) Per Cent
<i>Penicillin</i> 2,400,000 units in 7½ days (40,000 units × 60).	15.3	0	99.9
<i>Intensive Arsenotherapy</i> Mapharsen 1200 mg. in 5 days by intra- venous drip.	8.5	1 in 200 ¹²	96.5 ¹³
<i>Semi-intensive Arseno- bismuth Therapy</i> Mapharsen } 3 × 1 week } 12 (total } wk. 1200 mg.) } Bismuth } 1 × 1 week (to- tal 1.56 Gm.) }	3.5	1 in 2000 ¹²	37.5 ¹⁴

Penicillin Resistance. Dunham, Hamre and Rake¹⁵ have suggested, on the basis of animal experiments, that penicillin-resistant

strains may be developed by inadequate initial dosage. Tsun and Frazier,¹⁶ however, report that spirochetes (Reiter strain), exposed *in vitro* to gradually increasing concentrations of penicillin, do not become less susceptible to its antibiotic action.

Thus far at least, penicillin-resistant strains of *T. pallidum* have been no serious clinical program. The only report of early lesions failing to heal under penicillin therapy is that of Tyson,¹⁷ whose patient received 2.4 million units for seropositive primary syphilis over a period of *four days*, hardly a long enough time upon which to adjudge failure of response.*

On the other hand, lesions resistant to arsenobismuth therapy may heal satisfactorily with penicillin, as Nelson and Duncan¹⁸ have demonstrated in their report of six such cases from this clinic.

PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS

The major effort of the cooperative study thus far has been to define the usefulness of penicillin in the treatment of early acquired syphilis,¹⁹ and in this condition information of some statistical significance is now available. There are, in early syphilis, several well defined end-points from which conclusions may be drawn: (1) the disappearance time of spirochetes from infectious lesions, (2) the healing of lesions, (3) the attainment of seronegativity and (4) the incidence of clinical and serologic relapse, most of which occur within the first year.

How good is penicillin in the treatment of early syphilis? There can be, of course, no simple and unqualified answer to this question, for there are several factors which influence the results of therapy. Among these are: (1) the duration of the disease, (2) the time-dose relationships, (3) the total

penicillin dosage, and (4) the concurrent use of other antisyphilitic drugs.

Duration of Disease. As with all other forms of therapy, the earlier in the course of syphilitic infection penicillin is started the better will be the results. The common denominator appears to be the total number of invading organisms within the body of the host. In the cooperative study, the failure rate when the disease was of at least two months' duration was twice that among those treated within the first week of the disease. In the U. S. Army,²⁰ the failure rate in secondary syphilis was more than four times that of patients treated in the primary stage.

Time-Dose Relationships. There is ample evidence, both from the clinic²¹ and from the laboratory²² that the therapeutic effectiveness of penicillin is profoundly influenced by the method of its administration. In this respect, penicillin differs greatly from the arsenicals. The latter, being bound by the organisms of syphilis, are spirocheticidal in proportion to the amount of arsenic so bound,²³ which is in turn dependent upon the total quantity of arsenical to which the spirochetes are exposed. Thus, a higher arsenical concentration of short duration is as effective as a concentration half as great but maintained for twice as long.

Penicillin, on the contrary, is not bound by spirochetal organisms, and its activity depends upon *the length of time during which therapeutically effective levels are available* at the site of action. Precisely what the minimum effective level is and how long it must be maintained have not been determined. It is clear, however, that penicillin is actively spirocheticidal in extremely low concentrations. It also is evident that relatively low concentrations acting over a long period of time are far more effective than high concentrations of brief duration. Increasing the tissue levels of penicillin, by giving higher dosages per injection, tends to increase its

* We have recently observed a patient with a gumma of the penis that failed to heal with 4.8 million units of penicillin given over 15 days. The lesion healed promptly following therapy with mapharsen and bismuth.

therapeutic effectiveness in the treatment of syphilis, at least up to a certain point; but of far greater importance appears to be the time period over which *T. pallidum* is exposed to the action of the drug.

It has been presumed, largely from experiences with more acutely lethal infections, that in the treatment of syphilis it is desirable to keep the tissue levels of penicillin relatively constant throughout the course of treatment. Were this true, there would appear to be a theoretic advantage in administration by continuous infusion, either by intravenous or intramuscular drip. These methods, however, necessitate markedly restricted activity on the part of the patient, and may cause painful local reactions. In view of evidence²⁴ that blood levels following intermittent intramuscular injection are not markedly inferior to those of continuous infusion, and since satisfactory results have been obtained with the former method of administration, continuous parenteral administration seems neither necessary nor especially desirable.

Indeed, there is some evidence that constant maintenance of tissue levels may not be essential in the treatment of (experimental rabbit) syphilis. Eagle reports that in these animals, the interval between injections may be prolonged far beyond the usually recommended three-hour period without sacrificing therapeutic activity. He suggests that this is possible because *T. pallidum*, unlike many pathogenic bacteria, multiplies so slowly that a considerable period of time may elapse without a significant interim increase in the number of organisms. There is no clinical information to parallel this finding, although a favorable early response has been observed in small series of patients^{25, 26} treated on an ambulatory basis with aqueous solutions of penicillin, by schedules involving relatively long periods between injections during which no penicillin activity would be expected.

Total Penicillin Dosage. It is apparent from the above considerations that increased total dosages of penicillin will influence the results of therapy more if used to prolong the course of treatment than if given to augment the blood level at any one time.

With the time factor constant, the clinical results indicate a higher "cure" rate following 1,200,000 units than after 600,000 units. Results with 2,400,000 units are superior to those with 1,200,000, but the difference is less striking. With larger doses, there still are insufficient data, but with 4.8 million and 9.6 million units, it may be that the law of diminishing returns will become apparent.

Concurrent Use of Other Antisyphilitic Drugs. Eagle and his co-workers²⁷ have demonstrated that when penicillin and mapharsen are administered concurrently to syphilitic rabbits the therapeutic effects not only are additive but actually synergistic. A similar synergism between penicillin and bismuth also has been suggested.

This important laboratory observation has been studied by the clinics cooperating in the Penicillin Study, and the clinical results following the use of penicillin with mapharsen have been superior to those with penicillin alone.¹⁹ Administered in combination with bismuth, the results also are better than with penicillin alone. So significant does the U. S. Public Health Service consider this development that at its various Rapid Treatment Centers, the concomitant administration of penicillin, mapharsen and bismuth now is used routinely.

Recommendations for the Use of Penicillin in Early Syphilis. It is possible, on the basis of the facts now available, to outline in general terms certain recommendations for the use of penicillin in the treatment of patients with early syphilis. These are personal, and, as will be seen, involve both larger total dosage and longer duration of treatment than in previously published papers.

It is most convenient to start with an arbitrarily selected total penicillin dosage, which for seronegative primary syphilis should be a minimum of 3.0 million units; for seropositive primary syphilis, at least 5.0 million units; and for secondary syphilis, no less than 7.0 million units. Preparations with a minimal content of penicillin K are essential. Repeated intramuscular injections are preferred to other technics of administration.

With Aqueous Penicillin:

1. Hospitalization and administration throughout the day and night is desirable, if only to shorten the duration of treatment for the sake of convenience and case-holding.

2. Individual injections probably should not exceed 50,000 units. Further increases in the dosage per injection probably entail a progressive waste of penicillin.

3. A satisfactory interval between injections is three hours. When the time factor is important to the patient, the interval may be compressed to two hours, although perhaps at the expense of a slightly higher failure rate.

4. The total duration of treatment under these conditions would be *at least*: (1) seronegative primary, $7\frac{1}{2}$ days, (2) seropositive primary, $12\frac{1}{2}$ days, and (3) secondary, $17\frac{1}{2}$ days.

*With Penicillin-Oil-Beeswax:**

1. May prove to be feasible for use in the out-patient clinic and in the physician's office.

2. Tissue concentrations can be maintained for reasonably long periods of time in most cases with single daily intramuscular injections of 300,000 to 600,000 units each.

* It should be stressed that as yet there are available no significant data to support *any* arbitrary scheme for the use of POB in the treatment of syphilis. Unit for unit, POB may, in my opinion, be expected to prove inferior to comparable amounts of aqueous penicillin given in divided doses every two to three hours. Hence, not only should larger amounts of POB be used, but the total duration of therapy should be longer than with aqueous penicillin.

3. Occasional brief (twenty-four-hour) lapses in treatment (e.g., on Sundays when hospital clinics are closed) theoretically should detract little from therapeutic effectiveness.

4. The total duration of treatment probably should be at least: (1) seronegative primary, 10 days, (2) seropositive primary, 17 days, and (3) secondary, 23 days.

Whether metal chemotherapy should routinely be given concomitantly with the course of penicillin is largely a matter of personal preference. There is ample evidence that the combination is more effective than is penicillin alone. It is recognized, however, that the administration of arsenicals introduces a risk of serious reactions in direct proportion to the total amount of the drug, and in inverse proportion to the time interval over which it is given.

In view of this and other considerations, opinion is divided as to the desirability of combining penicillin and mapharsen in the routine treatment of early syphilis. The opinion of a majority of a group of competent syphilologists¹⁹ acting in an advisory capacity to the National Institute of Health is that the results of penicillin alone, when administered in adequate amounts over a long enough period of time, are satisfactory in a sufficiently large proportion of patients to justify eliminating arsenicals from the *original* course of treatment, reserving its use for relapsing cases. Schoch and Alexander²⁸ believe that a combination of penicillin and bismuth offers a satisfactory compromise, one which increases therapeutic effectiveness without significantly adding to the risks of therapy.

Whatever schedule of therapy is used in the treatment of early syphilis, it is essential that the outcome be determined by frequent post-treatment observations. Follow-up studies, including careful examinations for clinical evidences of relapse and serial *quantitative* serologic tests, should be made monthly during the

first year, and at gradually increasing intervals thereafter. The spinal fluid should be tested approximately six months following the completion of treatment.

Effect upon the Evolution of Syphilis of Small Doses of Penicillin. In penicillin a drug effective against both syphilis and gonorrhea is available for the first time. This fact raises the cogent question of the effect upon simultaneously acquired syphilitic infection of small doses of penicillin such as are used in the treatment of gonorrhea.

There is evidence that small doses of penicillin may either (1) prolong the incubation period and delay the serologic response, (2) modify or suppress completely the early tissue reaction, or (3) actually abort the disease.

Under these circumstances, patients with gonorrhea who also have suggestive signs of early syphilis should not receive (small doses of) penicillin until the possibility of a dual infection can be excluded. The presence of pre-primary syphilis should be seriously considered when patients receiving penicillin therapy for gonorrhea develop a constitutional reaction with fever, headache and malaise, which often is indicative of a Herxheimer reaction.^{29,30}

All patients treated for gonorrhea with penicillin should be followed for at least four months, and periodically checked with examinations to detect clinical manifestations of early syphilis and with reliable serologic tests.

PENICILLIN IN NEUROSYPHILIS

A proper evaluation of the results of therapy in neurosyphilis requires: (1) an understanding of its spontaneous evolution in the absence of treatment of any kind, and (2) a valid comparison between groups of treated and untreated patients. Neither of these two requisites can be entirely fulfilled. The course of untreated neurosyphilis is imperfectly understood, and there is avail-

able no group of untreated patients upon which to base a valid comparison. Moreover, there are few objective measures of "improvement" upon which penicillin can be compared with older forms of treatment.

The problem of evaluating the results of therapy in neurosyphilis is not new. It was well recognized by Wagner-Jauregg and his associates as they sought to assess the results of malarial therapy. Years of study convinced them that the efficacy of treatment in neurosyphilis should be determined solely by the response of the cerebrospinal fluid, and not at all by the clinical data, the proper interpretation of the latter being a matter of extraordinary difficulty. In the spinal fluid, the cell count and total protein content appeared to be of greatest significance, for in their experience, clinical progression rarely was observed when these two tests were normal.

Thus the concept of spinal fluid "activity" evolved, so ably championed by Dattner, Thomas and Wexler³¹ as the only satisfactory expression of the adequacy of treatment in neurosyphilis. Briefly expressed, the "Dattner-Thomas concept" is, that if the spinal fluid cell count and protein become and remain normal following treatment, the active process in the central nervous system has been rendered inactive and non-progressive, regardless of whether there has been any manifest clinical improvement. Such patients, they believe, need not be re-treated. Contrariwise, if treatment fails to reduce the spinal fluid cell count and protein content to normal, or if, having once become normal, one or both of these tests again become abnormal, the process within the central nervous system is considered to be "active." The patient, thus potentially subject to progression or relapse, requires further treatment.

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Effect of Penicillin upon Cerebrospinal Fluid Abnormalities. Therapy with penicillin results in improvement in the spinal fluid

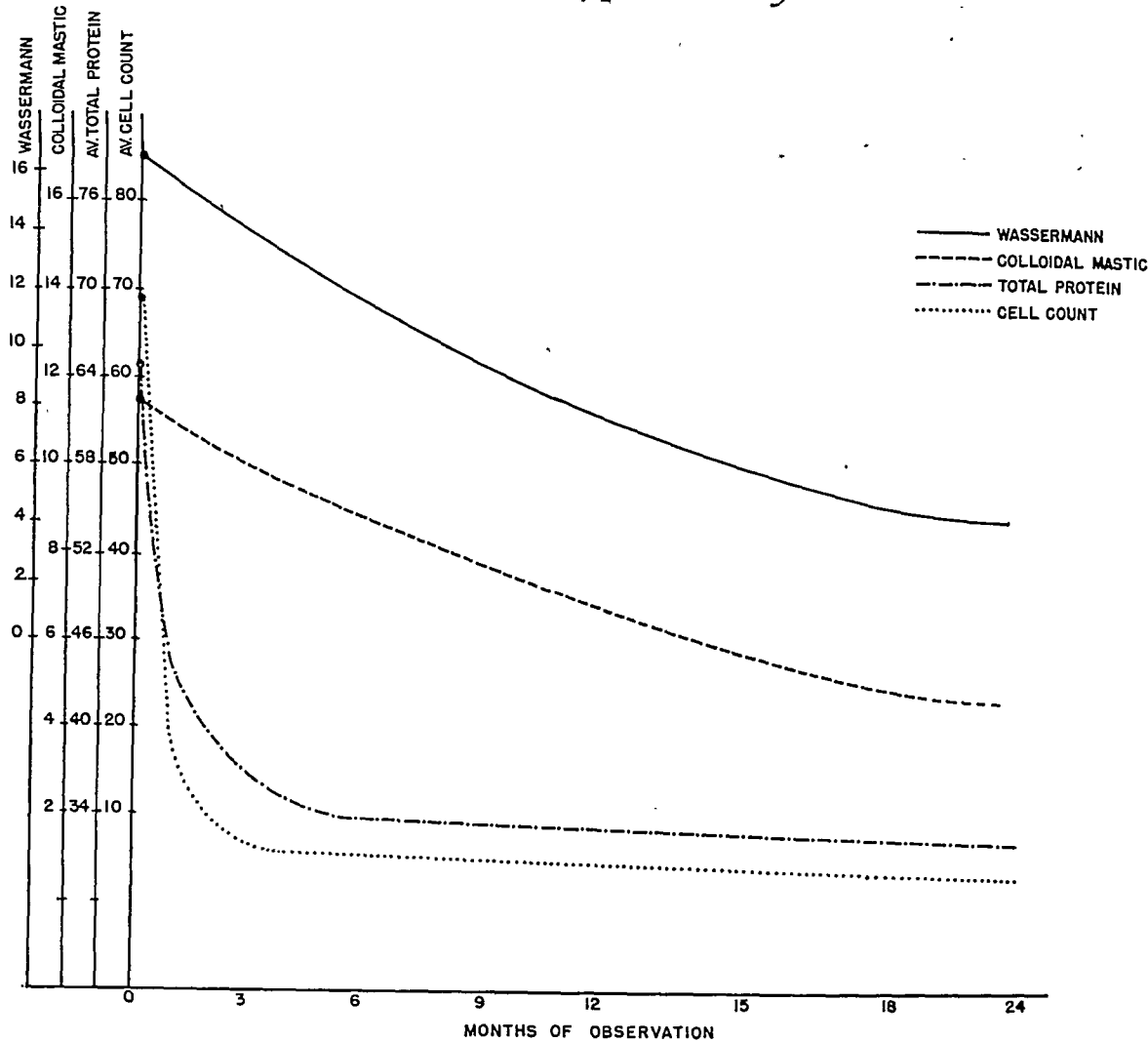


FIG. 2. Changes in spinal fluid abnormalities (all neurosyphilis) following treatment with penicillin alone.

abnormalities of neurosyphilis. This improvement is observed in a high proportion of patients treated, the immediate effect being approximately equally favorable regardless of the type of neurosyphilis.* It has been generally well sustained, at least during the limited period of observation so far available.

The changes in the spinal fluid follow a fairly regular pattern. (Fig. 2.) Elevated cell counts and total protein determinations become normal promptly, usually within a few weeks. This is followed by far more gradual but equally well sustained improvement in the results of colloidal tests and in the Wassermann titer.

Thus, as a result of penicillin therapy the

* With the possible notable exception of Erb's spinal spastic paraplegia.

evidences of "activity" rapidly and almost invariably disappear from the cerebrospinal fluid. Not in all cases, however, does the fluid remain inactive. In the series of patients at the Johns Hopkins Hospital, spinal fluid relapse six or more months after treatment has occurred in approximately 7 per cent of those who have been under observation for at least that period. Reactivation of the spinal fluid has been noted more frequently among those with symptomatic (usually parenchymatous) neurosyphilis (9.4 per cent) than among those with asymptomatic involvement of the neuraxis (4.4 per cent).

Asymptomatic Neurosyphilis. In patients whose only evidence of neurosyphilis is a positive spinal fluid, the results of therapy can be adjudged only by: (1) the post-

Penicillin in Syphilis—Reynolds

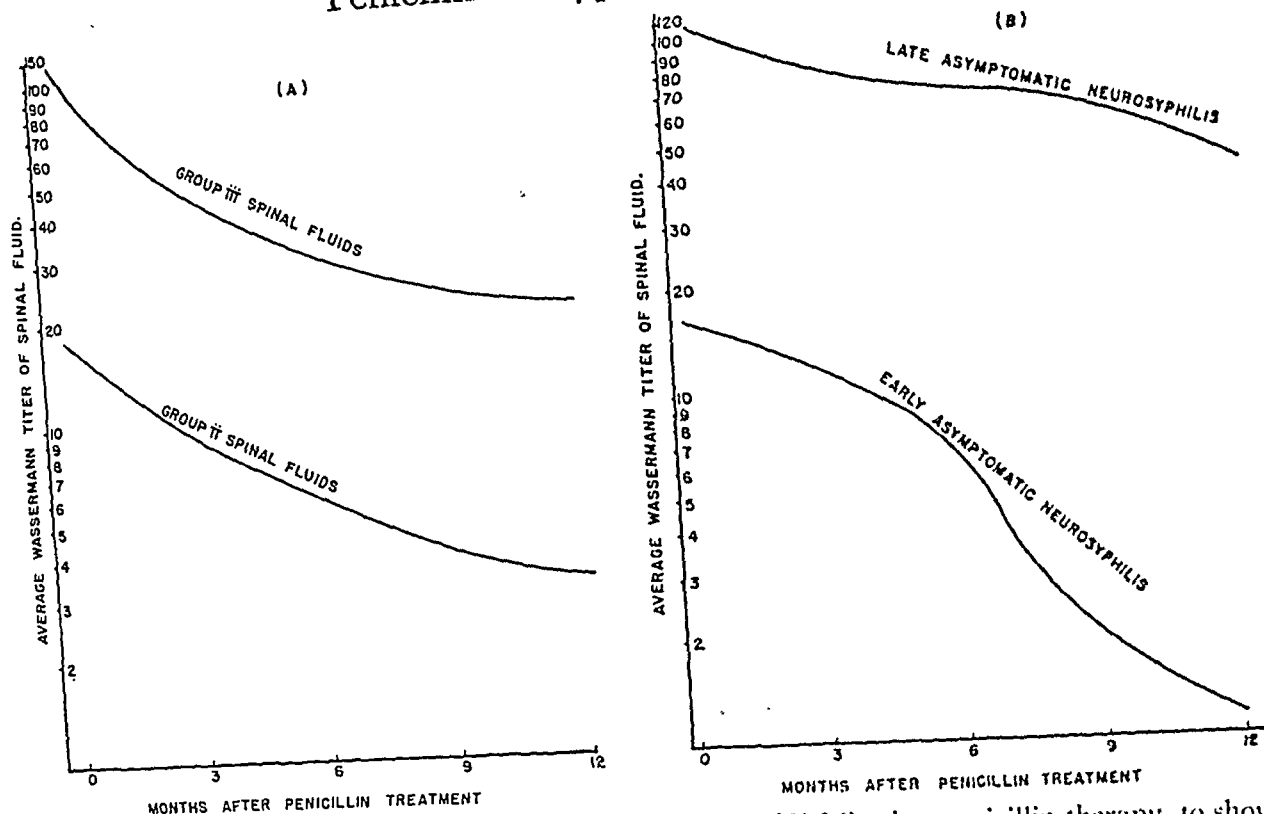


FIG. 3. Average spinal fluid Wassermann titer (arbitrary units)³² following penicillin therapy, to show the influence of; (A) degree of pre-treatment abnormalities and (B) duration of syphilitic infection. JHH data, smoothed curves.

treatment response of the spinal fluid, and (2) the incidence of progression to clinical neurosyphilis.

The early effect of penicillin upon the spinal fluid has been distinctly encouraging. Moore and Mohr,³² who recently summarized this clinic's first two years' experience, believe "... that penicillin exerts a profoundly favorable effect on spinal fluid abnormalities in early and late asymptomatic neurosyphilis; that this is manifest, in order of promptitude and extent, on cell count, protein content, colloidal test, and, last of all, on the complement fixation (Wassermann) reaction. . . . Within the brief time limits of this study [average duration of observation, 9 months], and keeping in mind the small number of cases involved [91], spinal fluid normality, once achieved, seems usually to be stable."

In asymptomatic neurosyphilis, the *rapidity* with which the spinal fluid becomes normal following penicillin therapy is dependent upon two factors: the degree of the pre-treatment abnormalities, and the dura-

tion of the syphilitic infection. (Fig. 3.) Lesser degrees of abnormality and those occurring within the first two years of syphilitic infection disappear rapidly; those more extensive and of longer duration improve slowly over a period of years.

The ultimate result in terms of clinical progression will not be known for many years. If, however, the Dattner-Thomas concept is valid for asymptomatic neurosyphilis, and if the favorable spinal fluid responses thus far noted, sustained, the incidence of clinical neurosyphilis developing in this group of patients should be low.

Effect of Penicillin upon the Clinical Manifestations of Neurosyphilis. However great may be the difficulties in evaluating clinically the results of penicillin therapy in symptomatic neurosyphilis, it is desirable to attempt an over-all approximation. Surely the patient is more interested in how much relief he may expect from his lightning pains or from his mental disturbance than in the cell count of his spinal fluid.

To this end, an attempt has been made to determine from the Johns Hopkins Hospital material what proportion of patients with various forms of neurosyphilis are considered to have been "improved" as a result of penicillin therapy. Details may be found in the several recent reports from this clinic,^{33,34,35,36} which summarize the early experiences with penicillin in various forms of neurosyphilis.

Sufficient material has been studied to allow a preliminary estimate of the results in acute syphilitic meningitis, general paresis (including taboparesis), tabes dorsalis, and Erb's spinal spastic paraplegia. (Table II.)

TABLE II
EARLY RESULTS OF THERAPY WITH PENICILLIN ALONE
IN CERTAIN FORMS OF NEUROSYPHILIS

	"Im- proved" Per Cent	No Change or Worse Per Cent
Acute syphilitic meningitis ³³	100	0
Paresis and taboparesis ³⁴	46	54
Tabes dorsalis ³⁵	37	63
Erb's spinal spastic paraplegia ³⁶ ..	0	100

No significant conclusions can yet be drawn in respect to diffuse meningovascular neurosyphilis, syphilitic epilepsy, primary optic atrophy or nerve deafness, although a few patients in each of these categories have been treated.

It is apparent from Table II that the results of penicillin therapy in acute syphilitic meningitis are excellent, but in parenchymatous neurosyphilis the results are not outstandingly favorable. Such improvement as occurred was attained, however, without subjecting the patient to the considerable dangers inherent in fever therapy.*

* In expert hands, the mortality rate from malarial therapy is approximately 1 per cent, from mechanical fever, as high or higher. The percentage of deaths due to fever treatment is inversely proportional to the care used in selecting patients for this rigorous form of therapy and the skill and experience of the attending physician.

There are sound reasons for combining fever with penicillin in the treatment of neurosyphilis. The combination of two effective forms of treatment might be expected to be superior to either alone. Moreover, the spirocheticidal activity of penicillin is known³⁷ to be enhanced at fever temperatures.

The concurrent administration of penicillin with malarial fever therapy appears, from the experience with general paresis,³⁴ to offer the patient with late parenchymatous neurosyphilis the greatest promise of a favorable outcome. It is the treatment of choice, therefore, in those forms of neurosyphilis which carry a serious risk to life or vital bodily function: paresis and taboparesis, primary optic atrophy and nerve deafness (in late acquired or congenital syphilis).

For the various syndromes of neurosyphilis, the initial treatment of choice, in the light of information now available, is as shown in Table III.

TABLE III INITIAL TREATMENT OF CHOICE IN THE VARIOUS SYNDROMES OF NEUROSYPHILIS	
PENICILLIN ALONE	FEVER PLUS PENICILLIN
Acute syphilitic meningitis	General paresis and taboparesis
Early asymptomatic neurosyphilis	Primary optic atrophy
	Nerve deafness (in late acquired or congenital syphilis)
Late asymptomatic neurosyphilis	
—Group II	
—Group III	→ (?)
Diffuse meningovascular neurosyphilis	
—Group II	
—Group III	→ (?)
Tabes dorsalis	→ (?)
	Erb's spinal spastic paraplegia

The therapeutic problem in tabes dorsalis and in Erb's spinal spastic paraplegia requires further consideration. In each, the outlook ultimately is for distressingly chronic invalidism. Since the evolution of these con-



FIG. 4. A, gumma of the palate before and B after treatment with penicillin (Dexter and Tucker³⁹).

ditions is gradual, with no immediate threat to life or vital bodily function, and since these patients frequently are in such poor general physical condition as to be poor fever therapy risks, it is not unreasonable first to try a form of therapy (e.g., penicillin) which is completely safe, provided there is any reasonable prospect that such therapy may be beneficial. In tabes dorsalis there is such a prospect, but in Erb's spastic paraplegia there appears not to be any.

In any form of neurosyphilis in which penicillin is given as the initial course of treatment, the outcome should be carefully reviewed within six months. If there has been no improvement within that length of time, none may be expected. Re-treatment, usually with malaria (plus penicillin?) may then be indicated, especially if there is evidence of "activity" in the cerebrospinal fluid.

PENICILLIN IN THE TREATMENT OF OTHER MANIFESTATIONS OF SYPHILIS

Benign Late Syphilis. The healing of³⁸ the lesions of benign late syphilis affords a most convincing demonstration of the value of

penicillin in the treatment of syphilis. Dexter and Tucker,³⁹ who have studied twenty-one patients with benign late gummatous syphilis in this clinic, report entirely favorable results. In eighteen cases, cutaneous, mucocutaneous or mucosal gummas were present; four of the patients had osseous lesions, and two, gummas of the liver. In these patients the clinical response was uniformly favorable. Cutaneous and mucosal gummas underwent rapid and progressive improvement (Fig. 4) after penicillin therapy, there being only one incipient relapse and one treatment failure in the entire group. The lesions of both of these two patients healed completely following a second and more intensive course of penicillin. Late syphilitic lesions of the skeleton and of the liver appeared to respond favorably to penicillin.

Cardiovascular Syphilis. Evaluation of the usefulness of any therapeutic agent in cardiovascular syphilis involves many years of post-treatment observation. There is, therefore, little information as to the results of penicillin in this important late manifesta-

tion of the disease. We have observed in a few patients some amelioration of the presenting symptoms (precordial pain, dyspnea) following treatment with penicillin. How much of this symptomatic improvement may have been due to hospitalization, bed rest and sedation is difficult to assess.

Caution has been urged⁴⁰ in the use of large doses of penicillin in the presence of cardiovascular syphilis in view of possible complications from therapeutic shock. This reaction has not been a serious problem in the limited series of patients coming under our own surveillance.

Latent Syphilis. In the treatment of latent syphilis, the purpose is to prevent the development of late manifestations of the disease. How adequately this can be accomplished with penicillin will not be known for several decades.

The only rationale for treating patients with latent syphilis with penicillin is by analogy. Since the drug possesses spirocheticidal action, and since it promotes the healing of manifest lesions, it is not unreasonable to expect that it *may* avert late complications if given at a time when the infection is clinically latent.

It is obvious, however, that treatment with penicillin offers nothing to those whose serologic test remains positive following adequate⁴¹ metal chemotherapy. To subject this group of patients to further therapy of any kind is to kindle false hopes and to waste time, money and effort.

Early Congenital Syphilis. In infants with congenital syphilis, penicillin appears to be at least as effective* as in early acquired syphilis in adults.^{42,43,44} There obtain the same therapeutic considerations, especially in regard to time-dose relationships, although the total penicillin dosage and the

* The incidence of infectious mucocutaneous relapse thus far has been significantly lower in infants with early congenital syphilis than in adults with early acquired syphilis.

size of each injection may be reduced in proportion to the body weight.

Infants with early congenital syphilis often are seriously ill. To add to their already precarious condition, therapy which in itself may be toxic, is highly undesirable. To the extent that penicillin is almost completely devoid of untoward reactions (save alone Herxheimer effects, which only occasionally appear to constitute any serious hazard), it is preferable to older forms of therapy.

There is the additional and highly important consideration of proper pediatric care, with especial attention to adequate hydration and nutrition, and the recognition and treatment of intercurrent infections.

Syphilis in Pregnant Women. In the prevention of prenatal syphilis through treatment of pregnant women with syphilis, penicillin has been highly efficacious.⁴⁵ Here it may well be, as Goodwin and Moore⁴⁶ suggest, the therapy of choice.

Penicillin readily passes the placental barrier⁴⁷ and its spirocheticidal action thus is available to the fetus *in utero*. It appears, despite the contention of some,^{48,49} not to provoke uterine contractions and not to precipitate labor.⁴⁹ No abortifacient effect of the drug has been apparent in the group of patients treated in this clinic.

The outlook for a non-syphilitic child following penicillin therapy during pregnancy is excellent. Even among those mothers whose syphilitic infection has been recently acquired, and in whom the risk to the child is great,⁵⁰ there have been remarkably few treatment failures. Because of the possibility of redissemination of organisms in the course of an infectious relapse, frequent post-treatment observations throughout the remainder of pregnancy are imperative.

SUMMARY

In penicillin there is added to the armamentarium of the syphilotherapist a drug

which is of negligible toxicity, readily administered, but with definite limitations in therapeutic effectiveness. It is far from being the ideal form of treatment; yet it is more than a fad. It has, for the present at least, a place in the treatment of syphilis as the most desirable form of therapy presently available for certain of the protean manifestations of this disease and as an adjunct to older methods in others.

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Combined Staff Clinics

Rheumatoid Arthritis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. CHARLES RAGAN: We would like to discuss a group of diseases which, while very different in some respects, have certain important characteristics in common. This group includes serum sickness, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, rheumatoid arthritis and scleroderma. It is now the fashion to classify these diseases together as disorders of the mesenchyme because they all show pathological changes in connective tissue, with clinical signs usually centering upon the joints and contiguous tendon sheaths, but with microscopic evidence of changes in muscle tissue, the subendothelial tissue of blood vessels and the endocardium, and the connective tissue of the myocardium.

Clinically, too, there is considerable overlapping. For example, it may be difficult to tell whether a given patient has rheumatic fever, rheumatoid arthritis or lupus erythematosus disseminatus. The following cases illustrate some of these points.

The first patient is Mrs. S. I believe you can all see that she has typical fusiform fingers with some limitation of motion of her wrists. The onset of her disease was fairly acute, in January, 1946. She came to us in June, 1946, after rather ineffective treatment. At that time—in June—she was in a wheelchair, confined to her home with flexion deformities of both elbows and both knees. She had a moderate hypochromic anemia. Her blood showed an elevated sedimentation rate and gave a positive agglutination test with group A hemolytic

streptococci. We wish to show her as a patient with rheumatoid arthritis in a remission. She has been treated with whole blood transfusions, gold and curare. At the present time she has no flexion deformities, she is able to do her own housework and drives a car.

The second patient is Kathie P., who is now nine years old. She has been sick since 1943. In December, 1943, she had a sore throat followed in two weeks by polyarthrititis. At the time she was in another hospital where she had definite pericarditis with effusion. She was first seen in the Babies Hospital in June, 1944, by which time she had developed flexion deformities of both wrists and both knees, and had by x-ray loss of joint space in both wrists. Throughout this period she had episodes of fever up to 105°F., which sometimes responded to salicylates and sometimes did not. In 1945 and 1946, she was in the hospital on three or four occasions and at the present time the disease process is still active, with an elevated sedimentation rate and some flexion deformities.

Kathie is to us an example of what is called Still's disease, which is essentially rheumatoid arthritis in childhood. In this age group you see the greatest interrelation between rheumatic fever and rheumatoid arthritis.

The third patient recently came to autopsy. In 1936, two weeks after delivery, she developed polyarthrititis with pericarditis. In 1936, 1937, 1938 and 1939, she was

seen at various times at another hospital with episodes of fever. She had several attacks of pleurisy and two bouts of pneumonia. In 1939, while in the hospital, she was observed to have a definite "butterfly" rash on the face. In 1941, she developed ankylosis of the wrists with persistent joint pain and subluxations of the proximal phalangeal joints. In 1943 and 1944, she received some chrysotherapy at the Presbyterian Hospital, and in 1945 she received Bogomolets' serum, all without benefit. In 1946, she was given adequate chrysotherapy, again with no improvement, and she was transfused with whole blood. In August, 1946, she was admitted to Presbyterian Hospital in cholemia and died. I have a picture of her showing the "butterfly" rash. Another picture shows her hands, which are as characteristic of rheumatoid arthritis as any we have seen. A biopsy of the gastrocnemius muscle in 1945 showed a small perineural lymphocytic nodule and at autopsy the characteristic lesions of lupus erythematosus disseminatus were found to be widespread.

These cases illustrate the clinical and pathological overlapping in the diseases which we would like to consider as a group. We are not clear about the pathogenesis of any of these diseases. Most of the work done in this field in the past has been in the nature of clinical classification. Today we are not concerned so much with classification as with an attempt to clarify the common denominator of the whole group, namely, the pathological lesion located in the mesenchymal or connective tissue.

We might begin our discussion with a summary of recent progress in the chemistry of connective tissue. Dr. Karl Meyer, who has contributed so much to our understanding of the mucopolysaccharides and mucoproteins, is here to present this phase of the subject.

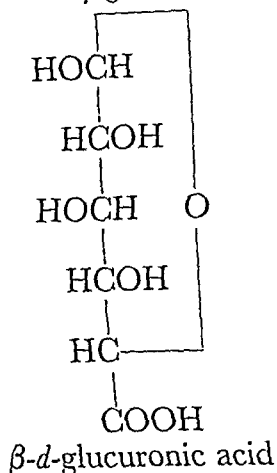
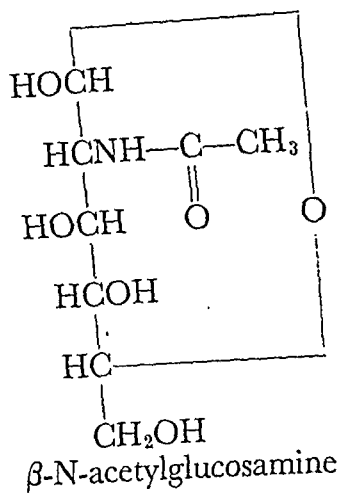
DR. KARL MEYER: Connective tissue is

composed of two major structural components, the fibrous elements and the cement substances. The two components belong to quite different classes of chemical substances, the fibrous elements being denatured, insoluble, fibrous proteins of very high molecular weight; whereas the cement substances are compounds or complexes of protein with highly polymerized mucopolysaccharide acids.

The fibrous elements fall into three main groups histologically: collagenous fibers, reticulin fibers and elastic fibers. Collagenous and reticulin fibers are said to be identical in origin and probably have the same chemical structure. The differentiating feature of the two, namely, the silver impregnation of the reticulin fibers, is attributed to closer packing of the fibrils but may, however, be due to a higher concentration of strongly reducing groups in the polysaccharides of the cement substances, as compared with collagen fibers. Collagen and elastic fibers both have a high glycine and proline content but differ in their content of other amino acids. Study by x-ray and electron microscopy of collagen fibers in tendon, loose connective tissue, skin and cornea has revealed a fine crystalline structure of the constituent fibrils, with alternating bands of higher and lower density spaced at regular distances from each other. By heating in aqueous solution, the crystalline collagen is converted into soluble and amorphous gelatin. Rat-tail tendon and all embryonic collagen fibers are soluble in salt-free dilute acids, forming extremely viscous solutions, as Nageotte has shown; while all other collagen fibers are insoluble in these solvents. The cause of this difference in solubility is unknown. On addition of salt or on neutralization, the proteins in these solutions precipitate as fibers which possess the same fine structure as the native fibers. Native adult collagen fibers are digested by pro-

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teolytic enzymes at a very low rate, comparable to the digestion of other fibrous proteins, like keratin.



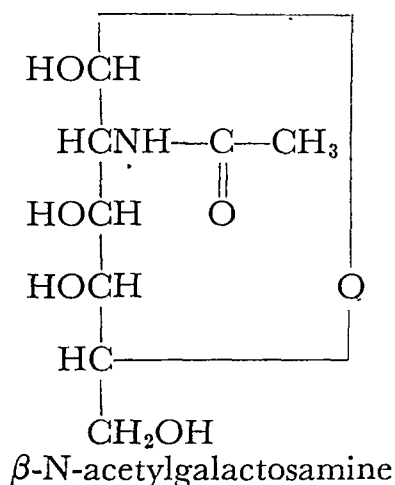
The interfibrillar or cement substances seem to be of considerable importance in the mechanism of rheumatic diseases, and will be discussed in some detail. According to the fundamental studies of Klinge, the primary lesions in rheumatic fever and rheumatoid arthritis are located in the interfibrillar spaces, while the swelling, fragmentation and finally lysis of the fibers is a secondary phenomenon. The chemical nature of the proteins of the cement substances is unknown. The mucopolysaccharides which are more or less loosely bound to the proteins have been studied more extensively. Up to the present time four mucopolysaccharides have been identified as components of cement substances, (1) hyaluronic acid, (2) hyaluronosulfuric acid, which has been found only in cornea,

(3) chondroitin sulfuric acid, and (4) the sulfuric acid ester occurring in amyloid tissue. The latter may be a component of normal mesodermal tissue which accumulates in excessive amounts in amyloid disease. It appears to be derived from heparin.

Hyaluronic acid is a polymer of a disaccharide composed of N-acetyl glucosamine and glucuronic acid. Its exact structure, like that of other mucopolysaccharide acids, is still unknown. The molecular weight of hyaluronic acid varies according to the source from which it is obtained; it has been estimated as between 200,000 and 500,000, and may be even higher. Hyaluronic acid occurs in vitreous and aqueous humor, in Wharton's jelly of umbilical cord, in synovial fluid, in skin and in some mesodermal tumors. In micro-organisms, it has been found only in group A and C hemolytic streptococci, when the organisms are in the mucoid phase. Mucoid phase and hyaluronate production have been correlated in some types with invasiveness of the organisms and with their resistance to phagocytosis and to destruction by whole blood. All attempts to produce antibodies against hyaluronic acid have failed.

Hyaluronic acid is depolymerized and hydrolyzed by specific enzymes called hyaluronidases, which occur in micro-organisms such as pneumococci, streptococci, staphylococci and in gas gangrene-producing organisms. Among animal sources the enzyme has been found in snake venoms, in the leech, and (in very high concentration) in the mature mammalian testis, or, more specifically, in spermatozoa. In the latter, the enzyme facilitates the depolymerization of the mucoid ground substance of the cumulus cells of the ovum, thus preparing it for fertilization. The greatest store of hyaluronidase in the mammalian body seems to be the skin where, however, it appears to be largely in an inactive form.

A very interesting property of hyaluronidases is their effect on dermal diffusion, the so-called spreading reaction of Duran-Reynals. This reaction usually is carried out in rabbits or in guinea pigs, but also has been observed in man. On intradermal injection of an indicator together with suitable concentrations of enzyme, the indicator diffuses in the skin over a wide area as compared to the localized bleb in control injections of indicator without hyaluronidase. The spreading reaction has been demonstrated also in the wall of the stomach and intestine, in muscle, fasciae and tendon. However, in contrast to skin, no hyaluronic acid has been isolated thus far from these sources.



Chondroitin sulfuric acid has a molecular weight similar to that of hyaluronic acid. It is a polymer of a disaccharide composed of equimolar concentrations of N-acetylgalactosamine, glucuronic acid and sulfuric acid, the latter apparently in the C₆ position of the galactosamine. Chondroitin sulfuric acid has been isolated from hyaline cartilage, from umbilical cord and from skin. A fraction recently isolated from calves' tendon is probably also chondroitin sulfate. It should be noted that two tissues contain hyaluronate and chondroitin sulfate in about equal concentrations, namely, skin and umbilical cord. Synovial fluid, vitreous humor and the tumor fluids contain only

hyaluronate, while cartilage contains only chondroitin sulfate.

Chondroitin sulfates probably are mixtures of similar but not identical compounds, some of which are hydrolyzed by hyaluronidases or by enzymes associated with hyaluronidases. The spreading effect in some tissues thus may be due to the hydrolysis of chondroitin sulfate rather than to that of hyaluronate. The metachromasia of some dyes (such as toluidine blue) shown by connective tissue and cartilage appears to be caused by chondroitin sulfate. Hyaluronate does not seem to be stained by any of the usual methods.

The known data of the chemistry of the connective tissue, when considered in relation to what has been learned by histological and tissue culture studies, suggest the following mechanisms in the development of connective tissue: The young, growing fibroblasts secrete hyaluronic acid, which is followed by the secretion of chondroitin sulfate and of a precursor of collagen, the latter a non-fibrous and soluble protein. By local acidification in the immediate neighborhood of the fibroblasts, the precursor is denatured by the polysaccharides, the latter acting as anionic detergents rolling up the peptide chains along the acidic groups of the fibrous polysaccharide molecules. Most of the hyaluronate is removed enzymatically, leaving the more firmly bound chondroitin sulfates as a network on the surface of the fibers. The latter by crosslinking grows into the mature insoluble fibers.

The pathological chemistry of connective tissue is still in an embryonal state. However, some insight into this field might be gained by recent studies (in collaboration with Dr. Ragan) on synovial fluid which embryologically, and to some extent physiologically, is related to connective tissue. The concentration of hyaluronate was measured by a turbidimetric method in

normal and pathological synovial fluids. Pathological fluids in this reaction appear as a stable colloidal turbidity, while normal fluids of man and cattle precipitate as a fibrous clot containing the polysaccharide. This clot formation is prevented by one hundredth of a unit of hyaluronidase, an amount too small to decrease measurably the hyaluronate concentration. With normal vitreous humor a colloidal precipitate is obtained, while in aqueous humor 95 per cent of the total hyaluronate is found in depolymerized, non-precipitable form. This depolymerization is due to the co-presence of hyaluronidase, which was demonstrated in a concentration of about 0.4 u/cc. in ocular fluid.

In synovial fluid no measurable amount of hyaluronidase could be demonstrated, unless the colloidal precipitation is taken as an indication of the presence of the enzyme in low concentration. The viscosities of over thirty synovial fluids examined were not directly proportional to the hyaluronate concentrations, the viscosities being higher and the hyaluronate concentrations lower in normal fluids as compared with pathological synovial fluids, obtained chiefly from cases of rheumatoid arthritis. In view of the increased volume of fluid in these pathological joints, they contain a considerably larger total amount of hyaluronic acid. In other words, the injured synovial cells apparently produce an excess of the acid, which may be followed by a compensatory increase of hyaluronidase, the source of which is undetermined.

Similar changes may occur in other mesenchymal tissue spaces leading to an increase in interfibrillar cement substances. Such an increased concentration of highly viscous material would presumably slow down metabolic processes.

DR. RALPH H. BOOTS: What is the relation of "mucin" and "mucine" to hyaluronic acid and hyaluronidase?

DR. MEYER: The term "mucin" in classical usage means any viscous secretion which on acidification with dilute acetic acid gives a ropy precipitate. Synovial fluid, which contains hyaluronic acid in considerable concentration, shows this phenomenon and is therefore said to contain "mucin." However, the "mucin" precipitated in this way is an artefact since the native hyaluronate of synovial fluid is not bound to protein, as shown by electrophoretic studies. Vitreous humor and some cystic tumor fluids also contain hyaluronic acid but often fail to give a precipitate with acid. The low protein or high salt content of these fluids is responsible for their failure to precipitate. Gastric mucin contains two mucopolysaccharides which are unrelated to hyaluronic acid. Salivary mucin, too, contains no hyaluronic acid.

The term "mucine" has also been used to denote different enzymatic reactions, such as depolymerization of the mucopolysaccharide of synovial fluid (hyaluronic acid), the liquefaction of salivary mucus, etc.

I think it would be best either to drop the ambiguous terms "mucin" and "mucine" or to use them only in a non-chemical sense.

STUDENT: Vitamin C has been shown by Wolbach to be essential for the growth of connective tissue. How does vitamin C fit into your concept of connective tissue development?

DR. MEYER: There is no definite information on the rôle of ascorbic acid in the genesis of the fiber. The sensitivity of some of the chondroitin sulfates to alkali and oxygen, and their ultraviolet spectra, suggest that ascorbic acid or a derivative of it may actually be a component of chondroitin sulfate, perhaps replacing some of the glucuronic acid units.

DR. RAGAN: We now would like to turn to one of the group, rheumatoid arthritis.

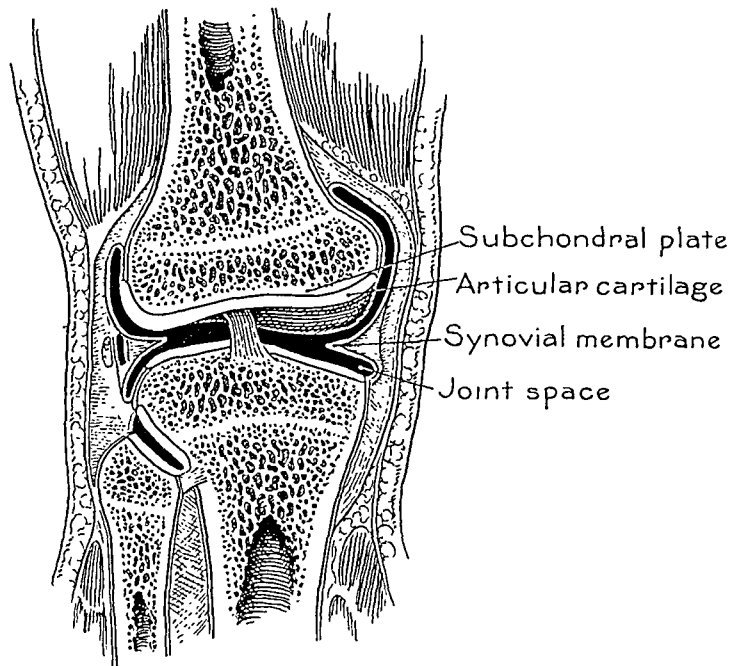


DIAGRAM OF DIARTHRODIAL JOINT
FIG. 1.—(After Callender.)

This is a severe progressive disease. It is of great social and economic import and various public health surveys have shown that chronic arthritis is a major cause of suffering and economic loss. Until recently rheumatoid arthritis was considered a disease purely of the joints. In the past ten years, however, evidence has accumulated which indicates that the disease is more generalized. Dr. Flynn of the Department of Pathology has been asked to discuss the morphological changes which are found.

DR. JOSEPH F. FLYNN: As has been stressed by previous workers, rheumatoid arthritis is indeed a protean disease, a disease whose clinical course may be characterized by remissions and exacerbations, a disease whose onset may be acute or insidious, a disease which may attack the individual at any age, a disease which may progress with incredible rapidity producing what has been aptly called the rheumatoid derelict, or again a disease which after a brief course may end abruptly, disappear and never return again.

The systemic pathology of this disease is almost as varied as are its clinical manifestations. By "systemic pathology" I mean the

lesions of the kidney, the bladder, the lymph nodes, the eye, etc. There are, however, a number of locations in which the changes are remarkably constant and it is on these that I will chiefly dwell. These locations are the joints, the nodules of the subcutaneous tissue, the nerves and the muscles.

Joint Pathology. Before demonstrating the pathology of the rheumatoid joint, I will review very briefly the anatomy of the diarthrodial joint. The anatomy of diarthrodial joints is essentially the same regardless of their location, whether the hand, wrist, foot, shoulder, knee, etc. The bones constituting the joint are covered by a layer of hyaline cartilage, called the articular cartilage. (Fig. 1.) It rests on a thin layer of dense bone known as the subchondral plate. You will recall that the joint cavity is lined by a continuous membrane, the stratum synovale or the synovial membrane. This is a layer of specialized connective tissue. It begins at the margin of the articular cartilage, covers the intra-articular portions of the bones and is reflected on the capsule to end at the margin of the opposite articular cartilage. Microscopically, the surface of the synovial membrane is thrown up into a number of tiny villous projections. This gives the membrane great flexibility, permitting it to be stretched for a considerable distance.

The synovial membrane is made up of collagen in which are imbedded the synovial cells—the modified fibroblasts. Intermixed with connective tissue, are a number of blood vessels, a few lymphatics, a few nerves and a few wandering cells. The structure of synovial membrane is essentially the same regardless of its location. However, the tissue on which it rests may vary.

The primary lesion of rheumatoid arthritis is an inflammation of the synovial membrane. It becomes enormously thickened by edema, hyperemia and inflammatory cell infiltration. As a result of



FIG. 2. Subacute villous synovitis from a case of severe rheumatoid arthritis. The stratum synoviale is enormously widened by edema, hyperemia and inflammatory cell infiltration.

edema there is often seepage of fluid out into the joint and this together with the increased activity of the synovial cells accounts for the great increase in joint fluid. This increased joint fluid stretches the capsule, often producing pain.

Figure 2 shows the rather typical appearance of the inflamed synovial membrane. Note the enormous widening of the membrane and the exaggeration of the villous projections. In the hypertrophic villi are collections of lymphoid cells. Some years ago an orthopedist, describing the pathology of rheumatoid arthritis, found collections of lymphocytes so arresting that he stated they were absolutely specific for rheumatoid arthritis. This is but another example of the all too frequent attempt to create pathological specificity on the basis of insignificant morphological alterations. Needless to say, there is nothing pathognomonic about it. They are found in a number of conditions.

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FIG. 3. Subacute villous synovitis with pedunculation of one of the villi. Often these pedunculated villi become necrotic and separate away to form free bodies within the joint. Note the increased vascularity, widening of the tissue spaces and inflammatory cell infiltration.

Often in rheumatoid arthritis the hypertrophic villi become pedunculated as seen in Figure 3. If these pedunculated villi become necrotic, they separate away to form free bodies in the joint space. Large amounts of fibrin are often deposited on the surface of the membrane or in the membrane itself. The fibrin is eventually organized and adhesions may result. In severe cases the inflamed synovial membrane may project into the joint space to form a pannus that creeps across the cartilage, like ivy grows across a wall. As it creeps across, the articular cartilage is destroyed. Now, and now only, excluding osteoporosis and swelling of the soft tissue, does roentgenographic evidence become apparent. This evidence consists first of a narrowing of the joint space due to disintegration of the articular cartilage. In severe cases, often simultaneously with the formation of the pannus, granulation tissue forms just beneath the subchondral plate.

Figure 4 is a section through the distal end of a normal femur. It shows a portion of the articular cartilage, beneath which is the subchondral plate. Below the subchondral plate are narrow spaces normally occupied by fibro-fatty tissue. In severe rheumatoid arthritis granulation tissue is present in the marrow spaces just beneath



FIG. 4. A section through the distal end of a normal femur. Above is a portion of the articular cartilage, resting on a layer of compact bone called the subchondral plate. Below is the fibro-fatty marrow.

the subchondral plate. The proliferation of the granulation tissue destroys the osseous trabeculae and the subchondral plate. When this occurs the articular cartilage is attacked from above and below, above by the pannus and below by the granulation tissue. If this occurs in both bones, the end result is a bridge of granulation tissue that stretches across the joint space. In time the granulation tissue becomes converted into fibrous tissue, producing a fibrous ankylosis that eventually goes on to bony ankylosis. Figure 5 shows some of these changes. The articular cartilage is degenerated as manifested by its altered staining reaction, the disalignment of the cells and empty lacunae. Above the articular cartilage is a pannus. Below the articular cartilage there is dissolution of the subchondral plate. Near one margin the granulation tissue from below almost reaches the pannus.

Figure 6 is a section from a "burned-out"



FIG. 5. A photomicrograph of a section through a diarthrodial joint showing marked rheumatoid arthritic changes. Above is the pannus creeping across the articular cartilage. The cartilage is degenerating. Note its altered staining reaction of the cartilage, large lacunae and disorderly arrangement of the cells. Below the articular cartilage, granulation tissue has destroyed the subchondral plate and is replacing the cartilage.

case of rheumatoid arthritis. This patient had an ankylosis of the femur and tibia. Here there is complete destruction of the articular cartilage with replacement by dense connective tissue.

Figure 7 is a roentgenogram of a wrist joint showing severe rheumatoid arthritic changes. Note that the joint spaces of the metacarpals are destroyed. The joint spaces between the metacarpals, radius and ulna are bridged across by osseous tissue. It must be remembered that the entire sequence of events just enumerated does not always occur. In many cases the process simmers along with remissions and exacerbations, without much pannus formation and without much granulation tissue beneath the subchondral plate.

Subcutaneous Nodules. As Bennett and Bauer¹ point out, the nodules of the subcutaneous tissue have received a great deal of attention. These workers have stressed the point that they are probably the most

¹ BENNETT, G. A., ZELLER, J. W. and BAUER, W. Subcutaneous nodules of rheumatoid arthritis and rheumatic fever; pathologic study. *Arch. Path.*, 30: 70-89, 1940.



FIG. 6. A photomicrograph showing the end state of rheumatoid arthritis—fibrous ankylosis. Above is dense connective tissue. The articular cartilage is destroyed as is the subchondral plate. The granulation tissue has disappeared and the marrow spaces are occupied by fibro-fatty tissue.

specific lesion of rheumatoid arthritis. The nodules usually measure about 1 to 2 cm. in size. Basically they consist of connective tissue in which are a number of granulomatous lesions. As a rule there are about five granulomatous lesions in the plane of any given section studied. The granulomas are made up of a zone of necrosis, then a zone of inflammatory cell reaction and then a zone of connective tissue. The necrotic tissue is disintegrated collagen. The inflammatory reaction consists of large mononuclear cells. Often multinucleated giant cells are present so that the lesion resembles tuberculosis. Indeed these nodules are sometimes called tuberculosis by the misinformed.

Muscles and Nerves. In 1942, Freund²

² FREUND, H. A., STEINER, G., LEICHTENTRITT, B. and PRICE, A. E. Peripheral nerve in chronic atrophic arthritis. *Am. J. Path.*, 18: 865-893, 1942.



FIG. 7. A roentgenogram of the right hand and forearm showing marked rheumatoid arthritic changes. There is reduction of the joint spaces of the wrist and hand due to destruction of the articular cartilage. A bony ankylosis of the carpal bones has occurred involving all except the pisiform. Punched out areas of periarticular bone destruction are present in the distal end of the metacarpal bones. These are due to proliferating granulation tissue beneath the subchondral plate. There is marked ulnar deviation of the phalanges.

and his associates described what they called a specific, inflammatory nodule involving the perineurium of many nerves in rheumatoid arthritis. In 1945, Freund³ described similar lesions in the muscles. He called the lesions in the nerves "nodular perineuritis," and in the muscles "poly-nodular polymyositis."

Figure 8 shows a fairly typical lesion in the perineurium of a nerve, cut longitudinally. Basically the nodule consists primarily of lymphocytes. They may be small, consisting of only a few lymphocytes, or they may be large enough to be seen with the

³ FREUND, H. A., STEINER, G., LEICHTENTRITT, B. and PRICE, A. E. Nodular polymyositis in rheumatoid arthritis. *Science*, 101: 202-203, 1945.

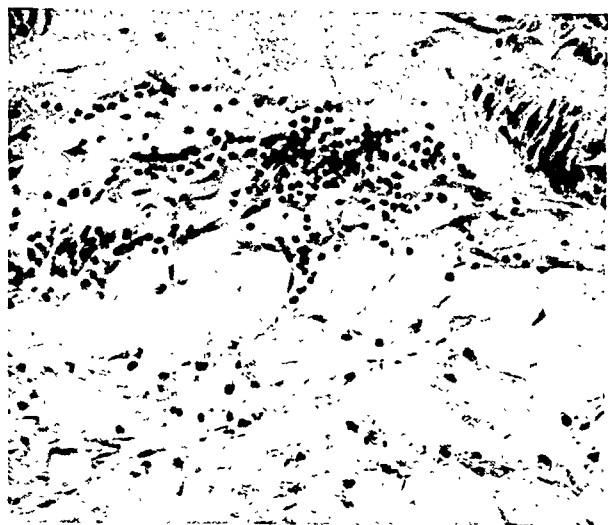


FIG. 8. A photomicrograph showing a nodular perineuritis. Near the top of the photomicrograph is a small nerve cut longitudinally. In the nerve is a dense collection of lymphocytes.

naked eye. Similar lesions⁴ are found in disseminated lupus and in dermatomyositis. Neither are the lesions in the muscles specific, since I have seen identical lesions in the atrophic muscles of poliomyelitis.

DR. RAGAN: The etiology of rheumatoid arthritis is unknown. I have asked Dr. Coss to review the present status of our knowledge of the relation of the hemolytic streptococcus to rheumatoid arthritis.

DR. JAMES A. COSS: Various organisms have at one time or another been implicated as the etiologic agent in this group of diseases without confirmation. At the turn of the century Westphal in Germany, and Poynton and Paine in England, directed attention to streptococci as a result of their cultural studies. This interest has been revived periodically by reports, from abroad as well as in this country, to the effect that a definite organism could be isolated from rheumatic lesions. Up to the present time numerous investigators have been unable to confirm these various reports. No one has succeeded in fulfilling Koch's postulates for any etiologic agent reported associated with rheumatoid arthritis.

Certain bits of evidence have served further to implicate the hemolytic strepto-

⁴ BAUER, W. Personal communication.

coccus, however. Todd has described an antistreptolysin test by means of which the titer of this streptococcus antibody can be measured. For practical purposes it is the antistreptolysin-O which is determined. It is elevated following acute hemolytic streptococcus infections, in nephritis, rheumatic fever and occasionally in the early stages of rheumatoid arthritis.

Cecil, Nichols and Stainsby described an agglutination reaction with group A hemolytic streptococci which was found to be positive in a high percentage of patients with rheumatoid arthritis. This was confirmed in our laboratory by Dawson, Olmstead and Boots. Since 1931, we have tested approximately 10,000 blood specimens for streptococcus agglutination. Fifty to 60 per cent of patients with rheumatoid arthritis give a positive streptococcus agglutination test. We have found a positive agglutination in fifty-six patients with diseases other than rheumatoid arthritis. Of these so-called "false" positives, twenty were in the group of the mesenchymal diseases.

In a review of fifty-six cases of juvenile rheumatoid arthritis⁵ we have found the median antistreptolysin-O titer to be 1 to 250, much higher than the normal maximum of 1 to 100 as read in our laboratory. Of all these patients tested, only three had a positive agglutination with group A hemolytic streptococci, as compared with a figure of 55 per cent positive in the adult disease. The absolute significance of such observations as these cannot be estimated until we know more about the agglutination reaction itself. It has recently been shown that the serum of some patients will agglutinate not only group A hemolytic streptococci but also non-specific particulate suspensions, such as unsensitized collodion particles (Wallis⁶). We are trying to clarify some of these points at present.

⁵ COSS, J. A. and BOOTS, R. H. Juvenile rheumatoid arthritis. *J. Pediat.*, 29: 143, 1946.

⁶ WALLIS, A. D. Personal communication.

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The streptococcus agglutination reaction probably is a non-specific test which, in our laboratory, has proven a useful tool in the study of arthritis. At times it fails to give a positive result in obvious cases of rheumatoid arthritis, very infrequently it gives false positive results, and the mechanism of the reaction is not clear.

STUDENT: Can rheumatoid arthritis be produced in experimental animals by injection of streptococci?

DR. COSS: Much of the difficulty in studying rheumatic disease has been our failure to reproduce the disorder in experimental animals. Streptococci injected intravenously into rabbits will cause arthritis, myocarditis and endocarditis; however, the lesions are not similar to the lesions seen in human beings. Such arthritis is not migratory, does not recrudescence spontaneously and is not self-perpetuating. In the cardiac lesions many similarities exist, but Aschoff bodies have not been described.

Rothbard produced arthritis in forty-five of fifty-one rats by injection of group A hemolytic streptococci from a case of septicemia and Rigdon was able to produce arthritis in rabbits by intra-articular injection of a staphylococcus toxin. None of these experiments, however, has resulted in an arthritis characteristic of the clinical picture as seen in human beings. Selye⁷ produced polyarthritis by treatment with adrenal cortical hormone but the technics necessary to bring about the lesions were quite vigorous.

Spontaneous arthritis has been observed in various animals, notably a polyarthritis of rats first reported and studied by Collier⁸ and assumed to be due to a pleuropneumonia organism; also arthritis in swine due

to the erysipelothrix (Collins and Goldie⁹), "strangles" in horses, and quite recently an arthritis in swine which seems to be caused by a virus (McNutt¹⁰). In these instances, and in many others which might be mentioned, it is possible to find as an exciting factor either an infectious agent or a deficiency in some food element, such as exists in the manganese deficiency sometimes responsible for lameness in swine.

DOCTOR: Since you include serum sickness, which has a well established allergic basis, as one of the group, is there any evidence that any of the others in the group has an allergic basis?

DR. COSS: It has been known for years that administration of heterologous serum in small amounts causes arthritis in 10 per cent of the recipients while large amounts cause arthritis in 90 per cent. It is possible to prevent or markedly diminish the arthritic component of serum sickness by the use of salicylates, and this is the one measure which also seems to benefit most victims of the rheumatic diseases.

Because of the implied allergic nature of one end of the spectrum of rheumatic disease (serum sickness), there has been much interest in the report of Klinge (1940) that it was possible to cause arthritis in rabbits by the repeated injection of horse serum. Rich¹¹ has reported that he was able to cause the lesions of periarteritis nodosa in rabbits also by the injection of horse serum.

Zinsser believed that acute rheumatic fever represented an allergic state for the following reasons: (1) the joint symptoms in anaphylaxis are more or less similar to those seen in articular rheumatism; (2)

⁷ SELYE, H. Hormonal production of arthritis. *J. A. M. A.*, 124: 201, 1944.

⁸ COLLIER, W. A. and STAVERMAN, G. J. The spontaneous polyarthritis of rats and the syndrome induced by inoculation of human material in these animals. *Ann. Rheumat. Dis.*, 2: 58, 1940.

⁹ COLLINS, D. H. and GOLDIE, W. Observations on polyarthritis and on experimental erysipelothrix infection of swine. *J. Path. & Bact.*, 1: 323, 1940.

¹⁰ McNUTT, S. H., LEITH, T. S. and UNDERBERG, G. K. An active agent isolated from hogs affected with arthritis. *Am. J. Vet. Research*, 6: 247, 1945.

¹¹ RICH, A. R. Hypersensitivity in pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. of Chicago*, 15: 270, 1945.

joint fluid cultures in articular rheumatism are usually sterile; (3) the joint lesions caused by injection of bacteria intravenously into animals are usually sterile; and (4) the sensitiveness of joints in experimental animals seems to some extent to run parallel to general sensitiveness. Against the theory of bacterial allergy in rheumatoid arthritis is the fact that no constant relation has been demonstrated between the organisms found and the skin reactions which the organisms in question afford. The sensitivity of the arthritic patients' skin to the nucleoprotein of strains of streptococci does not follow the course of the disease in all cases. Attempts at patient desensitization have failed. The following criteria of an allergic disease have not been fulfilled, namely, the determination of allergen by skin test or passive transfer of sensitivity, the disappearance of symptoms when the allergen is removed, the reappearance of symptoms on re-exposure to the allergen. If we try to enroll the hemolytic streptococcus as a bacterial allergen causing rheumatoid arthritis, it fails to fulfill the second criterion offered. We gave penicillin over a six months' period to ten arthritic patients in doses large enough to inhibit the hemolytic streptococcus but no change occurred in the course of the disease nor was there a change in the streptococcus agglutination reaction from positive to negative.¹² Similar attempts to eliminate the streptococcus by means of sulfonamides have failed in arthritis.

The Caveltis¹³ recently have prepared an antigen from ground-up human heart suspension which was used to coat collodion particles prepared according to the method of Cannon.¹⁴ A positive streptococcus agglu-

ination response with the sera of approximately 75 per cent of rheumatic fever patients was found when tested against this antigen. They previously demonstrated that auto-antibodies to kidney can be produced by immunization of animals with mixtures of group A hemolytic streptococci and kidney of the same species. This work has not as yet been confirmed, but in view of the close relationship of streptococcal infection and rheumatic fever, we are naturally much interested.

DOCTOR: What has been your experience with Bogomolets's serum in the treatment of arthritis?

DR. COSS: The anti-reticular cytotoxic serum, or ACS, which was developed in Russia was said to be of value in the treatment of various conditions including rheumatoid arthritis. Bach¹⁵ treated a group of patients without any appreciable benefit whereupon the originators of the serum said it was of value only in the second or allergic phase of disease. We have treated about thirty patients with this preparation with inconclusive results to date.

DR. RAGAN: It is often difficult to state confidently that such-and-such a patient does have rheumatoid arthritis. To us in the management of the patient, the most important practical problem in diagnosis is to differentiate whether the patient has rheumatoid arthritis or rheumatic fever. The joint symptoms of rheumatic fever are amenable to relatively simple treatment and rarely lead to deformity, whereas the joint manifestations of rheumatoid arthritis are, by and large, progressive and treatment should be so directed that progression is blocked and the deformities which lead to eventual crippling be kept at a minimum.

I would like to mention briefly the use of gold compounds. Gold compounds containing a sulfhydryl group were first used

¹² COSS, J. A., BOOTS, R. H. and LIPMAN, M. O. Prolonged administration of penicillin in arthritis. (In press.)

¹³ CAVELTI, P. A. Auto antibodies in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 379, 1945.

¹⁴ CANNON, P. R. and MARSHALL, C. E. An improved serological method for the determination of precipitative titers of antisera. *J. Immunol.*, 38: 365, 1940.

¹⁵ BACH, F. ACS serum in rheumatism. *Ann. Rheumat. Dis.*, 4: 62, 1945.

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in the treatment of rheumatoid arthritis in 1927, by Feldt in Germany. Forestier in France used gold extensively but it was not employed in this country until about 1938.

The treatment is purely empirical. The hypotheses upon which Forestier and Feldt based their rationale for treatment have not been substantiated. Much hostility has been raised towards gold because of the severe toxic reactions which are observed following its use.

Between 5 and 10 per cent of the patients with rheumatoid arthritis are unable to tolerate therapeutic amounts of gold because these patients develop a toxic reaction before an adequate amount of gold can be given. Of patients who have received full treatment, an average of 10 to 20 per cent show no improvement, 40 to 60 per cent show striking improvement with one or two courses. Follow-up studies reveal that at least 80 or 90 per cent of these patients relapse within five years, so that the response to gold constitutes a remission of the disease and not a cure.

It might be worth while to say that the relapse is not as severe as the original disease but, again, the response to treatment with gold after relapse is not as dramatic as the response to the first course.

I want to mention again what Dr. Flynn has stressed, namely, that this is a disease in which spontaneous remissions and exacerbations occur, and any form of therapy must be evaluated critically. However, in the experience of the Arthritis Clinic over a period of seventeen years, in which about 2,000 patients with rheumatoid arthritis have been seen, we have not found any therapy other than gold therapy which will consistently and in a high percentage of cases change the course of the disease. Since we believe that a relapse after gold therapy is to be expected, when a patient shows improvement and no toxicity it is our

present policy to continue administration of gold on a maintenance schedule.

Gold toxicity affects certain systems: the skin, as manifested by various pruritic lesions, with occasional severe exfoliative rashes; the gastrointestinal tract, with stomatitis or abdominal symptoms; and damage to the hemopoietic and renal systems. The stomatitis and renal damage may be due to overdosage, since these are similar to what is found in bismuth and other heavy metal poisoning, and we believe we can avoid these by smaller doses. The dermatitis cannot be predicted in any way. We do not know when to expect it. It may come early and it may come three to four months after the last gold has been given.

There is some encouragement in the use of BAL (British AntiLewisite) in the early treatment of toxicity but at the present time it is too early to evaluate these results. We can say definitely that with the administration of BAL there is a significant increase in excretion of gold in the urine.

The dosage schedule of gold compounds which we now employ is as follows: We use Solganol-B Oleosum, which is aurothioglucose. We start with small doses, 10 mg., and then increase to 25 mg. and, if tolerated, to 50 mg. at weekly intervals, and continue at 50 mg. weekly until the patient has received 1.0 Gm. of the compound. If the patient has shown improvement and has had no untoward toxic effect, the gold is continued, 50 mg. every two or three weeks. At the onset of any toxic manifestation, the gold is discontinued. Depending on the severity of the toxic reaction, gold may not be given again or it may be resumed in smaller amounts. We have not had the courage to resume gold following severe toxic reactions, such as a rash, so we cannot say that once a patient has had a severe reaction that patient is permanently sensitized to gold. It would appear that a patient who has had the disease for more

than two years is more likely to develop a toxic reaction than an early case. The toxic reactions can persist for long periods. Several of the dermatitides have lasted for over two years. We have had two deaths (in over 400 gold-treated cases) which could be attributed directly to gold, one due to aplastic anemia and the other to thrombocytopenic purpura.

Patients with rheumatoid arthritis and psoriasis respond less favorably to gold than those who do not have associated psoriasis. Rheumatoid arthritis of the spine, or ankylosing spondylitis of the Marie-Strumpell type, does not respond at all to chrysotherapy.

DR. PUTNAM C. LLOYD: Is there anything known of the mechanism of the action of gold in rheumatoid arthritis?

DR. RAGAN: The original work done by Feldt was begun because of the clinical similarity between rheumatoid arthritis and tuberculosis. In 1914, gold was found to be bacteriostatic and recently Dawson and Hobby showed that gold was bacteriostatic against group A hemolytic streptococci. Until the pathogenesis of the disease is more clearly understood, I am afraid we will know no more of the mechanism of the action of gold. We have suggestive evidence that relapse may be associated with the elimination of gold. We do know that gold must be combined with a sulfhydryl group to be effective. This may have a bearing on its mechanism or it may be due solely to the fact that gold compounds, to be soluble at a pH around 7, must be in the gold-thiol form.

STUDENT: Is there any way to avoid toxic reactions?

DR. RAGAN: We believe that we can decrease the incidence of stomatitis by not exceeding a weekly dose of 50 mg. of the compound. Hemopoietic toxicity such as thrombocytopenia and agranulocytosis can be kept at a minimum by frequent blood counts with estimation of the platelets on

the smear. Renal damage can be kept to a minimum amount by frequent urinalyses. The skin lesions are difficult to predict, some are preceded by an eosinophilia, some are not. All are preceded by a pruritus and at the first mention of pruritus, gold should be stopped. If the patient fails to develop a rash, we believe that by vigilance we may have avoided a severe dermatitis. However, most of the patients who develop pruritus go on to develop a rash of more or less severity even if the gold is stopped. We have a routine to which we adhere rather strictly. A patient receiving chrysotherapy has a white blood count with an estimation of platelets on the smear and a urinalysis every two to three weeks. I would again like to mention BAL, which promises to be fully as effective in combating gold toxicity as it is in arsenic and mercury poisoning.

DOCTOR: Do you believe that with adequate care, gold can be administered by the local medical doctor?

DR. BOOTS: We are somewhat reluctant to advocate the use of gold in general practice by physicians who have had no previous experience with it. Where we have sent patients from out of town back to their doctors with instructions on the administration of gold, we have found that more trouble developed than with patients we have followed ourselves. There are many alarms and excursions in the course of gold therapy and to evaluate these, it is important that the physician have considerable understanding of the eventualities which may develop. If a watch is kept over the blood count and urine and if gold is stopped at the first symptom of pruritus, sore mouth, or abdominal cramps, the physician who has not seen a lot of gold therapy should be able to carry out this form of treatment.

DR. RAGAN: The flexion contractures which develop in rheumatoid arthritis are a striking characteristic of the disease and the basis of many of the deformities. These, with the muscle atrophy and the micro-

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scopic lesions in the muscle described by Freund, have led us to focus our attention on the skeletal musculature.

We have been fortunate in interesting Dr. Schlesinger of the Neurological Institute in this problem, and have asked him to discuss it for us today.

DR. E. B. SCHLESINGER: I have been asked to discuss the problem of muscle spasm in rheumatoid arthritis. There are few terms in clinical medicine which are so misused or which can evoke so much controversy as muscle spasm. We ought, therefore, first define our terms. Loosely, muscle spasm is a reflex defense phenomenon, a prolonged contraction not amenable to voluntary control, characterized by resistance to stretch and by diffuse, severe, poorly localized pain. How does this state come about? There are many possible mechanisms which may act as the initial stimulus. First, we may have actual irritation of the sensory nerve endings in the muscle mass itself. This may be due to mechanical trauma or inflammatory exudate. Secondly, muscle spasm may represent protective splinting of a neighboring joint which is the seat of disease. Lastly, the abnormal state of contraction may be secondary to changes in other parts of the neural arc, such as in the posterior columns, posterior root or sensory ganglion. Pathologic changes in these structures may lead to hyperesthesia, pain and diffuse tenderness in the muscle, which reacts by an attempt at shortening and immobilization.

All this may be worthy of further clarification. Normally, muscle stretch elicits afferent impulses arising in the muscle spindles. These impulses are conducted back to the cord, and a reflex contraction is then initiated by way of the motor side of the arc. This is the basic stretch reflex of Sherrington. When there is pathologic change somewhere in the system, there may be a potentiation of this cycle. The threshold of the arc is lowered, and the response becomes much more active than under normal

circumstances. Thus we have the mechanism for a self-perpetuating circuit, the vicious cycle of pain and splinting or spasm. Attempted stretch elicits pain and further splinting, then more pain, and so on. Now that we have roughly defined the probable mechanism, we may turn to the problem at hand.

In acute rheumatoid arthritis, one is struck by the severity of the muscle changes. Here, in addition to joint inflammation (which causes reflex splinting) there may be infiltration of the actual muscle mass by inflammatory exudate. Also, there may be changes in the peripheral nervous structures themselves. Thus we find many of the elements which lead to muscle splinting or spasm and its accompanying pain and deformity. The acute arthritic limb adopts a flexion position which represents an attempt to avoid muscle stretching and joint irritation. These positions, a defense mechanism, may be easily reversible early, but if allowed to persist, may become a major cause of deformity. We know that long fixation leads to atrophy of disuse.

We must emphasize that in attempting to influence these phenomena, we are not attacking the primary disease entity but merely its secondary manifestations. Nevertheless, such changes may leave the patient crippled permanently, even though his primary disease be in complete remission.

How do we propose to handle such a situation? We know that any agent which acts by relieving pain or avoiding movement is useful in symptomatic relief. Any form of therapy which invades or breaks up the vicious cycle of pain and spasm may dramatically alter the clinical picture. Promotion of absolute rest has many dangers and needs no discussion here. Heat, analgesics, local anesthetic blocks, etc., are time-tried and respected forms of treatment. Unfortunately, none are specific or reliable.

In an attempt to attack the problem more basically, we have turned to drugs which

have a specific relaxant effect on muscle. Curare is such a drug. The initial difficulties in obtaining a suitable preparation being solved by the development of a long-acting suspension of curare in oil and wax, it is quite logical to try curariform drugs in an attempt to reduce reflex shortening with its concomitant pain. We have been using such a preparation in various syndromes which have in common the entity of muscle spasm. Our results are in the right direction but unquestionably open to criticism if any final conclusions were to be drawn so early in the work.

DOCTOR: What beneficial effects have you obtained with curare suspensions in oil and wax?

DR. SCHLESINGER: Our patients seem more comfortable. They show greater mobility. They do not adopt marked flexor protective positions. They may not require as much analgesia or sedation. They seem to respond better to physical therapy. These are all clinical impressions and therefore of little objective value. There are, however, objective data, too, which indicate a beneficial effect of curare. Perhaps the most important are electrical studies. Briefly, a muscle, at rest shows no electrical activity when studied by standard electromyographic technics. A normal muscle can be put at rest in full extension. Certain of our patients with rheumatoid arthritis, on the other hand, show consistent evidence of electrical activity, incident to reflex shortening, except in positions of pronounced protective flexion. We believe we can claim a therapeutic response when such patients gain full extension and in that position show no bursts of impulses representing attempted shortening. Such results are obtained with curare. The patient you have seen today (Mrs. S.) is a good example of the desired end result.

Another objective criterion is obtained by a study of urinary creatine output. During his visit here, Dr. Mortensen of Denmark

described to me his findings in a series of acute low back cases with severe muscle spasm. He was able to demonstrate a sharp rise in creatine output during the acute clinical phase and an abrupt fall in output when the clinical signs subsided. Adapting his technic to our problem, we have tried to study the changes which might occur in our patients with rheumatoid arthritis. There seems to be a rough correlation to date which may prove useful but much more work must be done.

DR. RAGAN: Gold is still a very controversial subject and curare is still new and experimental. However, there are certain broad concepts of treatment upon which I think almost everyone working in this field will agree and these should be stressed. Dr. Boots said he would talk about this part of the program.

DR. BOOTS: To state that we use chrysotherapy for rheumatoid arthritis often gives a wrong impression. It suggests that other forms of treatment have been discarded. Such is far from the truth.

Patients with early active disease are most suitable for gold therapy and best results are obtained in this group. Gold is discontinued immediately if any evidence of toxicity occurs. We do not like to administer gold to the elderly, to those with a history of liver or renal damage, or blood dyscrasia. Excellent results are not as frequent when the disease is advanced and marked deformities have occurred. Also, we hesitate to use gold for patients whose family physicians have advised strongly against taking it. We do not use gold if the disease is quiescent. For the reasons outlined, probably not more than 60 per cent of the patients with rheumatoid arthritis in our clinic are started on gold therapy and of this number 10 per cent receive inadequate gold treatment because of early development of toxicity. In addition to gold this group is treated with the more conservative measures which are used for the non-gold treated patient.

Combined Staff Clinics

What are these other methods of therapy? They consist chiefly of (1) measures which improve the general health of the patient, reduce fatigue, giving him a chance for spontaneous remission, (2) measures which give symptomatic relief, and (3) the prevention and correction of deformities.

The time allowed will not permit of detailed discussion of all of these, and we will limit ourselves to little more than their enumeration.

MEASURES WHICH IMPROVE THE GENERAL HEALTH OF THE PATIENT

A. Rest (or avoidance of fatigue) is almost as necessary for rheumatoid arthritis as for tuberculosis. The amount varies from complete bed rest for the severely ill patient who has a persistent fever, to an hour's rest period before dinner, or the simple avoidance of severe fatigue for the mildly ill.

B. Nutrition. The patient is usually thin and undernourished, sometimes to the point of emaciation, and a highly nutritious diet is essential. We frequently supplement such a diet with 2 tablespoonfuls of cod liver oil at bedtime. While it would seem sensible to give an abundance of vitamins, massive doses of any particular vitamin seems to be of no specific value. In recent years, vitamin D in capsules of 50,000 units have been widely and, in our opinion, unjustifiably recommended in advertisements. In our experience such preparations have been of no proven value in rheumatoid arthritis and sometimes result in severe and irreversible vitamin D poisoning.

C. Treatment of Anemia. Hypochromic anemia is frequently present and responds poorly to iron administration. Several transfusions of 500 cc. of blood to such patients will usually cause marked improvement.

D. Removal of Intercurrent Infections. Formerly there was thought to be a direct relationship between rheumatoid arthritis and foci of infection. We have been unable to prove any such relationship. However, the

eradication of infections, such as periapical abscesses and chronic sinus infections, helps the general health of the patient.

E. Climate. The prevalent opinion is that the disease rarely occurs in tropical climates. No well controlled experiment has ever been done of sending patients to the tropics but it would seem that this offers definite possibilities provided the patient can live as comfortably in such regions as in his home.

F. Psychotherapy. An optimistic attitude on the part of the physician is very helpful. These patients are easily depressed and it seems as though there is some relationship between their mental depression and increase in their symptoms.

MEASURES WHICH GIVE SYMPTOMATIC RELIEF

A. Analgesics and Sedatives. There is no proof that salicylates have any direct effect upon the course of rheumatoid arthritis but they offer considerable relief of the pain. Salicylates are of real value in giving the patient increased rest and comfort, and, as far as we can tell, do no harm.

B. Physiotherapy. Physiotherapy is of much more value for osteoarthritis than rheumatoid arthritis but it probably has no real effect upon the course of the latter disease. However, such measures as compresses or flaxseed poultices to a painful joint often offer relief.

PREVENTION AND CORRECTION OF DEFORMITIES

Much can be done by the internist in the prevention of contracture deformities by the use of posterior splints, applied for varying periods each day. These deformities are in large part due to muscle spasm and it may be that the use of curare in conjunction with exercises within pain limits as described by Dr. Schlesinger, will prove of equal value. The correction of deformities which have already occurred lies mostly in the

field of the orthopedic surgeon and will not be discussed at this time.

DOCTOR: I am not clear as to your opinions on the value of rest in the patient with rheumatoid arthritis.

DR. RAGAN: At the present time we believe that we cannot be too dogmatic upon this point. Rest has been one of the most trusted standbys in the treatment of rheumatoid arthritis and its value in diminishing pain, fever and evidence of activity of the disease process is unequivocal.

However, we believe that rest should be supervised. To tell a patient to go home to bed or to hospitalize a patient and prescribe strict bed rest can be very detrimental. The group at Cornell have shown that, in normal males with bed rest in a plaster spica, definite changes in the metabolism of the patient occur. Notably, a negative nitrogen balance sets in. Clinically, we know that muscle atrophy and osteoporosis are associated with continued inactivity. A patient with active rheumatoid arthritis confined to bed lies in a position of inactivity almost comparable to a body spica because of voluntary splinting of the painful joints. We believe that exercises within the limits of pain and fatigue can be carried out in such patients. In conjunction with adequate salicylate therapy to control pain and curarization to combat the element of muscle spasm the range of motion can be extended. This effort to decrease the muscle atrophy in rheumatoid arthritis is still in progress and a conclusive evaluation of the results cannot be made at this time but the preliminary results are encouraging.

SUMMARY

Rheumatoid arthritis is a common disease of unknown etiology, subject to remissions and exacerbations, characterized clinically by striking involvement of the joints and, to a varying degree of other systems, and demonstrated pathologically to be a disorder of connective tissue. Presenting certain

common features with rheumatoid arthritis are serum sickness, rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa and scleroderma. Despite clinical and pathological similarities, it is not implied that all these disorders have a common etiology.

The clinical picture of rheumatoid arthritis is well known. Cases are presented which serve to emphasize the multiplicity of systems involved as well as the overlapping of the other mesenchymal diseases in the clinical picture of rheumatoid arthritis.

Because the connective tissue appears to be the common denominator throughout this discussion, the nature of its two main subdivisions was considered. The three types of fibrous elements, collagenous, reticulin and elastic fibers are known to be denatured, insoluble proteins of high molecular weight. The cement substances on the other hand are made up of compounds or complexes of proteins with highly polymerized mucopolysaccharides. Hyaluronic acid, hyaluronosulfuric acid, chondroitin sulfuric acid and the amyloid sulfuric acid ester are the only four polysaccharides yet identified. All are of high molecular weight and their exact composition is unknown. Specific enzymes called hyaluronidases exist in the mammalian body, as well as in many other natural sources, which possess the specific power of depolymerizing and hydrolizing hyaluronic acid and perhaps other polysaccharides. While all these substances are presumably concerned with the diseases under discussion, their normal physiology and pathological variations have not yet been worked out.

In some patients with rheumatoid arthritis, hyaluronate is increased in the synovial fluid but what significance this observation has remains to be determined.

When considered pathologically, rheumatoid arthritis presents two chief charac-

teristics. One is the granulomatous lesion of connective tissue with necrosis, round cell infiltration, palisading and giant cell reaction contributing to nodule formation. This may be grossly seen subcutaneously about the elbows or may be only microscopically visible in the connective tissues of nerves, blood vessels and muscle. The other lesion is essentially the same but because it involves the connective tissues of joints—the synovial, capsular and subchondral tissues—results first in an acute inflammation and later in destruction of the joint. The clinical findings of redness, heat, swelling, pain, joint deformity, muscular spasm and atrophy, and subcutaneous nodules thus all have a common pathological basis. When this process is widespread the general manifestations of fever, weakness, anemia, weight loss, cardiac, renal, lymphatic and eye disease may also be understood.

Klinge has postulated that the initial lesion of rheumatoid arthritis involves the connective tissue cement substance. At the present time no etiological agent or mechanism is known. The hemolytic streptococcus theory has as yet resulted only in the diagnostic group A streptococcus agglutination reaction which is positive in about 55 per cent of cases of rheumatoid arthritis but which may be a non-specific reaction. As yet no virus etiology can be regarded as established nor has the possibility of allergy, bacterial or otherwise, though attractive, ever been placed on tenable grounds. Much of the difficulty lies in the fact that the disease as yet cannot be experimentally produced either in man or animal.

The problem of therapy is unsolved. The status of gold therapy is difficult to evaluate. Five to 10 per cent of patients develop early toxic reactions which preclude therapy. It may be possible to avoid stomatitis and renal damage by moderate dosage but the toxic reactions of the skin are unpredictable and not yet controllable. Ten

to 20 per cent of patients receive no benefit from therapy. Forty to 60 per cent are definitely improved but of these 80 to 90 per cent relapse in a five-year period. Continuous treatment with gold to avoid these recurrences is now being tried.

It is believed that in the early cases of true rheumatoid arthritis, gold is the best means of therapy. In the Edward Daniels Faulkner Arthritis Clinic at the Presbyterian Hospital, about 50 per cent of patients with rheumatoid arthritis do not receive gold therapy either because of contraindications to gold therapy or because it is refused by the patient. About one-half of these show some improvement, whether due to the general measures instituted or to a spontaneous remission. Supportive measures include those directed at improving the general health of the patient: adequate rest, high vitamin and caloric diets, transfusions and the treatment or removal of intercurrent disease. They include psychotherapy to attempt to ease mental burdens and adjust the patient to his disease. Heat, salicylates and sedatives may make the acute stages less difficult while physiotherapy and appliances to prevent and correct deformities tend to improve the latter situations. Finally, because of the rarity of the disease in the tropics, the removal of the patient to the tropics should be considered where the status of the patient permits.

One interesting approach, novel but promising, is the use of curariform drugs. Based on the premise of a self-perpetuating vicious cycle of pain and muscle spasm initiated by reflex stimuli from diseased joints, muscle or the nervous reflex arc, a long-acting preparation of curare in oil and wax is employed to induce relaxation of muscle. Clinical improvement seems to follow and objective studies by electromyographic technics and creatine excretion, which are still being evaluated, tend to be corroborative.

Clinico-pathological Conference

Chronic Granuloma*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. C., was a sixty-five-year old white male hotel executive, who entered the Barnes Hospital for the first time on February 12, 1946, complaining of generalized itching, cough and loss of weight. The family history was non-contributory. The patient stated that he had always been well until the onset of the present illness. Two years before entry he underwent bilateral inguinal herniorrhaphy without event. About eight months before admission he noted the onset of lacrimation which at times was intense; it was more pronounced on the left.

Six months prior to entry the patient developed a pruritic eruption on his legs. One month before admission the lesions became red and raised. The pruritus became generalized and so severe that the patient could not rest day or night. He was seen by a dermatologist who made a diagnosis of scabies but the lesions did not respond to specific treatment. Subsequently they resembled erythema multiforme and finally they took on the characteristic appearance of erythema nodosum. During the month before entry the patient noted increasing weakness and he felt feverish. His physician noted that he had temperature elevations as high as 101.6°F. on several occasions. During the six months before admission the patient lost 17 pounds. Two weeks before admission he had a sore throat

which persisted for several days. Concomitantly the patient developed a cough which was productive of thick mucoid sputum. He had several profuse sweats and an occasional slight chill.

On physical examination at the time of entry, the patient's temperature was 37°C., pulse 90, respirations 18, and blood pressure 140/70. He was an elderly man who appeared pale and chronically ill. There were numerous excoriations on the skin. Over the lower extremities, and to a lesser degree over the upper ones, red, raised, tender nodules, 2 to 3 cm. in diameter, surrounded by a zone of erythema, were present. A few lymph nodes were palpable in the left posterior cervical chain and large, firm, freely movable nodes were felt in both axillary and inguinal regions and in the left epitrochlear region. There was chemosis of the right eye and the conjunctiva was inflamed. The left eye was similarly involved but to a lesser degree. The pupils reacted normally to light and accommodation. The right fundus appeared normal; the left could not be visualized. The left auditory canal was filled with green, foul-smelling débris. The drum was thick and no landmarks were visible. No perforation was seen. The nasal mucosa was reddened. The throat appeared normal. The epiglottis was red and thickened; the left vocal cord was fixed in the cadaveric position. The

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lungs were clear to percussion and auscultation. The heart was not enlarged; the rhythm was regular. A harsh, grade II systolic murmur was heard at the apex and at the aortic area. The liver was felt 2 cm. below the right costal margin; neither the spleen nor the kidneys were palpable. The physical examination was otherwise within normal limits.

Laboratory data were as follows: Blood count: red cells, 3,400,000; hemoglobin, 10.4 Gm.; white cells, 7,100; differential count: eosinophiles, 11 per cent; stab forms, 1 per cent; segmented forms, 67 per cent; lymphocytes, 21 per cent. Urinalysis: negative except for an occasional red blood cell per high power field. Stool examination: negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; total proteins, 7.7 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 4.4 Gm. per cent. Blood culture: no growth. Heterophile agglutination test: negative. Sputum examination: no tubercle bacilli seen. Bone marrow: stimulation of myeloid cells with a shift to the left; 7 per cent plasma cells and 2 per cent reticulum cells were present. Cephalin-cholesterol flocculation test: 1+. Roentgenogram of the chest: "The cardiac silhouette is within normal limits as is the aorta. There is a plaque of calcium in the aorta. Hilus shadows are quite prominent suggesting large lymph nodes. Lung markings are somewhat coarse and feathered; they extend out from the hilus on both sides. The parenchyma is clear." Gastrointestinal series: indeterminate. Cholecystogram: normal gallbladder. Electrocardiogram: slight notching was present and there was a Q wave in Leads I and IV; interpretation: myocardial damage.

During his hospital stay the patient's temperature rose daily, usually reaching 39°C. and occasionally 40°C. The pulse rate rose and fell consistently with the

temperature curve; the respiratory rate was normal. Soon after admission, a lymph node was removed from the right axilla. The microscopic sections showed considerable hyperplasia of the lymphoid elements but the general architecture remained unchanged. A moderate number of eosinophiles was seen and there was some increase in fibrosis but no Dorothy Reed cells were visible. The epithelium was normal. A diagnosis of "reticular hyperplasia" was made.

The patient received repeated transfusions and was given a short course of roentgen therapy to the lymph nodes which gradually became smaller. The skin lesions varied in intensity but were never completely absent. Pruritus was a constant, distressing symptom. Shortly after admission, the patient's cough increased, and showers of crepitant inspiratory râles were heard at the base of the right lung. Penicillin therapy was given but the cough continued unabated. Many specimens of sputum were examined for tubercle bacilli but none were found. Numerous blood counts were not significantly different from those on admission except that the eosinophiles were reduced. Repeated cultures of the blood were sterile. A chest film taken about two months after entry showed considerable increase in the prominence of the hilar shadows on the right. The pulmonary markings were also accentuated in the right lung more than previously, and there was infiltration about the bronchial and vascular markings. Impression: "bronchopneumonia, right lung." The patient failed to improve, and on discharge he retained most of the symptoms present at the time of admission. He left the hospital on April 20, 1946.

He continued to do poorly at home; his fever persisted and the skin lesions did not improve. While at home he was given two injections of anti-reticular cytotoxic serum.

He reentered the Barnes Hospital on May 4, 1946.

At the time of entry, the patient's temperature was 38.3°C., pulse 90, respirations 24, and blood pressure 130/64. He appeared extremely ill; he was weak and emaciated. The skin was hot, generally atrophic and slightly icteric. Areas of brown pigmentation were noted over the trunk at the site of previous lesions. On the forearms there were several small movable nodules with slight surrounding erythema. One was present on the dorsum of the left hand. There were also pustules scattered over the skin. The auricle of the left ear was somewhat swollen, red and tender to the touch. Moderate contracture deformities at the elbows and knees were present. There was no significant lymphadenopathy. The eyelids were slightly swollen; the palpebral conjunctivae were pale and small pin-point yellow papules were present on their surface. Examination of the lungs revealed dullness to percussion, bronchial breath sounds and medium râles at the right base posteriorly. There was a soft, grade II systolic murmur at the apex. The liver edge was felt 4 cm. below the right costal margin. The spleen was not palpable. Neurological examination showed flattening of the right side of the face. The tendon reflexes were all hyperactive.

Laboratory studies were as follows: Blood count: red cells, 3,360,000; hemoglobin, 10.7 Gm.; white cells, 6,850; differential count: eosinophiles, 1 per cent; stab forms, 13 per cent; segmented forms, 55 per cent; lymphocytes, 28 per cent; monocytes, 3 per cent. Urinalysis: albumin, trace; sediment, occasional white blood cell per high power field. Stool examination: negative. Cocci-dioidin skin test: negative. Culture of skin pustules: non-hemolytic staphylococcus; cultures for fungi were negative.

The patient received anti-reticular cytotoxic serum and transfusions. His tempera-

ture ranged between 38°C. and 40°C. The skin manifestations noted on entry persisted; in addition, lesions characteristic of erythema nodosum recurred. A decubitus ulcer developed over the coccyx. A fluctuant, subcutaneous mass was noted in the left axilla from which thick pus was aspirated. The patient was discharged unimproved on June 1, 1946.

Because of the investigations on the treatment of lymphomas with nitrogen mustard compounds at another university clinic, the patient was transferred to that institution. There the physical findings were identical with those recorded on the patient's last Barnes Hospital admission.

Studies were as follows: Blood counts: unchanged from those noted previously. Total proteins, 7.1 Gm. per cent; albumin, 2.1 Gm. per cent; globulin, 5.0 Gm. per cent. Cultures of skin lesions for fungi: negative. Roentgenogram of the chest: "Enlargement of both hilar shadows, extensive pulmonary infiltration in both lungs, more on the right."

The skin lesions were biopsied and the sections were studied by several pathologists. No definite diagnosis was made but an "atypical lymphoma" seemed most likely. Because the diagnosis could not be definitely established, therapy with a nitrogen mustard derivative did not seem justified. The patient was given iodides with some improvement in the appearance of the skin lesions. He was discharged and returned immediately to the Barnes Hospital where he was admitted for the last time on July 5, 1946.

At the time of entry the patient's temperature was 39.2°C., pulse 130, respirations 40. He was emaciated, pale, and appeared *in extremis*. There was slight icterus of the sclerae. The skin was atrophic and large areas of brown pigmentation were noted. Numerous ulcerations including the decubitus over the coccyx were present. The

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tongue was red and dry. Signs of fluid were noted at the right lung base. Otherwise the physical findings were unchanged from those of the previous admission.

Laboratory data included the following: Blood count: red cells, 2,830,000; white cells, 2,750; differential count: eosinophiles, 2 per cent; stab forms, 38 per cent; segmented forms, 37 per cent; lymphocytes, 19 per cent; monocytes, 4 per cent.

The patient failed rapidly and died on July 6, 1946, twenty-four hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presented such a difficult problem that despite very thorough study a definite diagnosis could not be made during the patient's long illness. Four aspects of the illness were most prominent; first, the distressing pruritus and several skin lesions; second, the persistent fever; third, the lymphadenopathy; and finally, the hyperglobulinemia. Dr. Weiss, would you comment on the skin lesions and their relation to the underlying disease?

DR. RICHARD S. WEISS: I first saw this man in January, 1946. He complained of extreme pruritus but the skin lesions at that time were not striking. The only finding was the presence of excoriations which in some respects resembled those seen in scabies. The distribution of the lesions, however, was not typical of scabies. Nevertheless, I prescribed anti-scabetic treatment; the patient returned in one week and stated that he was very much better. He then developed urticaria and lesions characteristic of erythema multiforme. Subsequently erythema nodosum was noted. Several weeks later when I again saw him, he looked quite ill and complained bitterly of pruritus. His temperature was slightly elevated and there was alarming lymphadenopathy which led me to the conclusion

that the patient had a serious systemic disease, possibly Hodgkin's disease or one of the lymphomas. I therefore recommended that he be hospitalized for more detailed study.

DR. HAROLD SCHEFF: It is of interest that a differential blood count done at that time showed a 10 per cent eosinophilia.

DR. ALEXANDER: Do you attribute the eosinophilia to the skin manifestations, Dr. Weiss?

DR. WEISS: Eosinophilia occurs in many generalized skin diseases. In cases of lymphoma with involvement of the skin the eosinophilia is usually more profound than was recorded in this instance.

DR. ALEXANDER: It may be concluded, I presume from your observations, Dr. Weiss, that the patient definitely exhibited the lesions of erythema multiforme and erythema nodosum. Attention has been called to the fact that the patient had generalized lymphadenopathy and one of the nodes in the right axilla was removed for study. Dr. Moore, would you describe the microscopic sections cut from the surgical specimen.

DR. ROBERT A. MOORE: The first lantern slide (Fig. 1) shows a section of the skin removed. The thickness of the epidermis was approximately normal. There was slight edema of the dermis about the blood vessels and about some of the accessory structures of the skin not shown in the section. A cellular infiltration, consisting largely of the cells of the mononuclear series, was noted. The diagnosis on the basis of these findings was chronic inflammation of the skin. The second slide (Fig. 2) is that of a section of the lymph node; it shows the capsule of the node with the associated vascular and lymphatic spaces. There was hyperplasia of the follicles of the node, but the cellular types present within the node were normal, and there was only slight cellular infiltration of the capsule. The pathologic diagnosis was hyperplasia and chronic in-



FIG. 1. (No. 46-1194). Microscopic section of skin removed at the time of lymph node biopsy. The changes are those of chronic inflammation. $\times 47$.

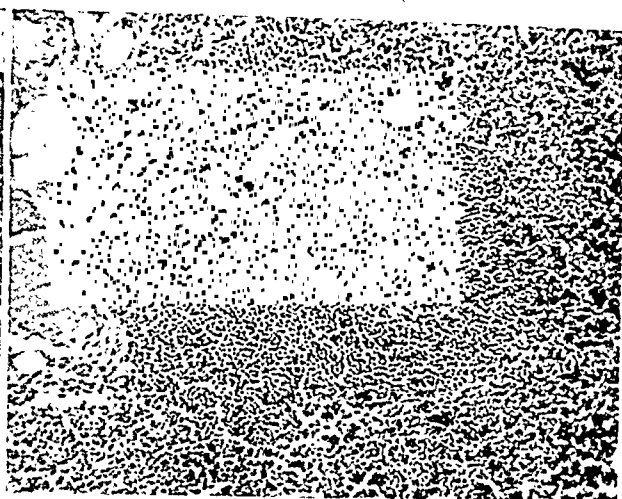


FIG. 2. (No. 46-1193). Microscopic section of lymph node showing follicular hyperplasia. $\times 47$.

flammation of the lymph node. In neither the skin nor the lymph node were there any changes characteristic of a specific disease entity.

DR. ALEXANDER: From the information available, Dr. Moore, do you believe that the diagnosis of lymphoma is likely?

DR. CARL V. MOORE: It is our opinion that either reticulum cell sarcoma or Hodgkin's disease was the most likely possibility. Against the former was the fact that the lymph node did not show characteristic changes; against the latter was the fact that the patient never had a lymphopenia. Although there is no definitive blood picture in Hodgkin's disease, frequently a lymphopenia is noted during some phases of the disease.

DR. ALEXANDER: Is it true that in Hodgkin's disease a leukocytosis may occur?

DR. C. V. MOORE: That is correct. The white cell count may range from a leukopenic level to counts of 150,000 or more.

DR. ALEXANDER: The bone marrow was reported as showing stimulation of the myeloid elements. Would you comment on the significance of this finding.

DR. C. V. MOORE: Myeloid stimulation such as was observed here is compatible with almost any inflammatory disease.

DR. ALEXANDER: If this patient had one of the lymphomas, for example lympho-

sarcoma, would the lymph nodes be expected to show characteristic histologic changes.

DR. EDWARD H. REINHARD: Yes, they would. However, I have seen instances in which the first lymph node biopsies from patients with lymphosarcoma or with Hodgkin's disease failed to show definitive lesions whereas subsequent biopsies showed the characteristic histological changes. In lymphosarcoma, however, there is usually tremendous proliferation of the lymphocytes with destruction of the architectural pattern and, very frequently, invasion of the capsule.

DR. ALEXANDER: Is it correct to say that frequently in Hodgkin's disease the characteristic lesions may not be seen in lymph nodes in certain phases of the disease whereas in lymphosarcoma, if there is lymphadenopathy, pathologic changes in the lymph nodes will be present in most cases.

DR. REINHARD: I think that is correct.

DR. ALEXANDER: Therefore, in this case, if a diagnosis of lymphosarcoma cannot be made from the microscopic sections of the lymph node removed from the patient's axilla, it may be inferred that in all probability the patient did not have lymphosarcoma. Dr. Moore, do you feel that the diagnosis of Hodgkin's disease is still tenable despite the lymph node findings?

DR. C. V. MOORE: Yes.

DR. ALEXANDER: The skin lesions were consistent with Hodgkin's disease. The fever was persistent for many many months. If there is high fever in Hodgkin's disease, is it necessarily of the Pel-Ebstein type or may it be continuous?

DR. C. V. MOORE: The fever is not continuous as a rule, but it may be.

DR. ALEXANDER: Would you agree that the blood picture and bone marrow findings do not suggest leukemia?

DR. C. V. MOORE: They most certainly do not.

DR. ALEXANDER: Dr. Scheff, you and Dr. Womack saw giant cells in the microscopic sections of the lymph node. Did you think that the findings in the section were compatible with a diagnosis of tuberculosis of the lymph nodes?

DR. SCHEFF: We did not think so.

DR. ALEXANDER: Dr. Goldman, would you comment on generalized lymphadenopathy in tuberculosis. Is there an adenopathic type of generalized tuberculosis, and if so, is it common?

DR. ALFRED GOLDMAN: Generalized lymphadenopathy does occur in generalized tuberculosis but it is not very common.

DR. ALEXANDER: Dr. Bottom, did the chest roentgenogram indicate to you that this patient had tuberculosis?

DR. DONALD S. BOTTOM: He has had tuberculosis, but I believe the present findings are indicative of a quiescent tuberculous lesion in the lungs.

DR. ALEXANDER: Does generalized adenopathy as a manifestation of tuberculosis occur in any particular age group?

DR. GOLDMAN: It may occur in patients at any age, but it usually occurs in patients in the younger age groups.

DR. ALEXANDER: It would be quite rare, then, in a patient as old as this one.

DR. GOLDMAN: Yes. That is one of the reasons why Hodgkin's disease seems more likely in this case. However, some of the findings are compatible with sarcoidosis

and that diagnosis should be considered. Generalized lymphadenopathy is common in sarcoidosis.

DR. ALEXANDER: The apparent enlargement of the hilar lymph nodes is also in keeping.

DR. GOLDMAN: I am not able to state whether the skin lesions seen in this patient are compatible with Boeck's sarcoid. Perhaps Dr. Weiss would discuss that point.

DR. WEISS: The skin lesions were not consistent with those seen in sarcoidosis. Usually the skin manifestations of sarcoid are moderately hard, flat plaques or nodules; they have no tendency to suppurate and they are usually situated adjacent to the joints.

DR. ALEXANDER: Are there other features in this case suggestive of sarcoidosis?

DR. W. BARRY WOOD, JR.: The eye findings certainly should be mentioned.

DR. ALEXANDER: That is a good point. We have no specific information about the uveal tract, but the eye signs were prominent in the clinical course.

DR. WOOD: In the cases of sarcoid described by Dr. Longcope, the initial symptoms were frequently related to the eye. That was true in this case. Further, it has been emphasized by many writers that the serum globulin tends to be extremely high in sarcoid, and I think that the hyperglobulinemia here is another point in favor of Dr. Goldman's suggestion. Against the diagnosis of sarcoid, however, is the relatively malignant course of this patient's illness. I would therefore postulate that if the patient had sarcoid, he probably had tuberculosis, too; the two diseases are not infrequently seen together at postmortem examination.

DR. ALEXANDER: Tuberculosis involving what organs?

DR. WOOD: I cannot specify where Dr. Moore will find the tubercle bacilli, Dr. Alexander, but I think active tuberculosis would explain the relatively rapid course of

the illness; sarcoid alone without tuberculosis usually runs a more benign course.

DR. ALEXANDER: Am I clear, then, that you believe the patient had both sarcoid and tuberculosis rather than tuberculosis alone.

DR. WOOD: Yes, I think that such a combination is likely in this case.

DR. ALEXANDER: Certainly sarcoid and tuberculosis occur together frequently; indeed some writers believe that they are the same disease.

DR. WOOD: Dr. Fitcher followed some of the cases of sarcoid in Baltimore, and I would like to ask him whether or not pruritus was a prominent feature.

DR. PALMER H. FUTCHER: I do not recall that it was.

DR. ALEXANDER: When sarcoid is complicated or followed by tuberculosis, does the tuberculous process occur at the site of the sarcoid lesion, or do they occur apart from one another?

DR. ROBERT A. MOORE: I belong to the group which believes that sarcoid and tuberculosis are two independent diseases. My answer to the question, therefore, would be that although tuberculosis may occur in a patient with sarcoid, the sarcoid lesions do not become tuberculous.

DR. ALEXANDER: Dr. Reinhard, would you discuss the anti-reticular cytotoxic serum which this patient received.

DR. REINHARD: Anti-reticular cytotoxic serum is prepared by immunizing animals—horses or rabbits—with a mixture of human bone marrow and lymph node or spleen. The serum presumably contains antibodies against human reticulo-endothelial cells. Bogomolets, who developed the serum, claims that small amounts stimulate the reticulo-endothelial tissues of the body, whereas larger doses are destructive. He advocates the use of the serum as a means of avoiding the changes of senility, and also in treating diseases of the reticulo-

endothelial system; in the latter he advises larger doses in order to destroy those tissues.

DR. ALEXANDER: Would you comment on the clinical experience with the serum.

DR. REINHARD: There have been extremely few clinical results reported; most investigations to date are reported in the Russian literature. In this country there is confirmatory evidence, from experimental work, that the serum does have a potent antibody which will affect the growth of reticulo-endothelial cells in tissue culture.

DR. ALEXANDER: Is it generally available?

DR. REINHARD: No. We obtained it from a commercial laboratory which supplies it for investigational use only, and we were told very little about the method of preparation. We were told only how much of the serum to give, at what interval to give it, and that the treatment should not be repeated in less than six weeks.

DR. ALEXANDER: What about experience with the nitrogen mustard compounds in Hodgkin's disease and other lymphomas?

DR. REINHARD: The evidence published to date indicates that the nitrogen mustards have a definite beneficial effect in Hodgkin's disease and perhaps in other lymphomas. The remissions which are induced by nitrogen mustards do not last as long as those following x-ray, and the compounds are certainly at least as damaging to other normal structures as x-ray; I believe that most of the investigators who are studying the nitrogen mustards now feel that they may be useful in cases resistant to x-ray. However, one should emphasize that such patients rapidly become resistant to nitrogen mustard also.

In regard to the diagnosis, Dr. Alexander, either a fungus infection or tuberculosis seem very strong possibilities to me.

DR. ALEXANDER: The possibility that this patient was afflicted with a fungus infection was entertained very seriously. Cultures were made on Sabouraud's media

but were unrevealing. Likewise coccidioidin skin tests were done. In regard to tuberculosis I should like to ask if erythema multiforme occurs commonly in tuberculosis.

DR. WEISS: Not commonly, but it is seen occasionally.

DR. ALEXANDER: It has been taught that when one sees erythema nodosum, one must think of rheumatic fever or tuberculosis. Actually, erythema nodosum may be seen with a variety of infections.

DR. ROBERT ELLIOTT: It has been pointed out that uveo-parotid fever may be one of the manifestations of Boeck's sarcoid; however, I believe that erythema nodosum is not common in sarcoidosis.

DR. PAUL O. HAGEMAN: It seems to me that there are two points supporting the diagnosis of neoplasm in this case; one, the paralyzed vocal cords; and two, lymph nodes which receded with x-ray therapy. These two points lead me to favor the diagnosis of Hodgkin's disease.

DR. CARL V. MOORE: Dr. Alexander, a thorough search was made for acid-fast organisms in this man's sputum and none was found. Likewise the bone marrow preparations were examined for acid-fast organisms with negative results. I would like to ask whether the lymph nodes were stained for acid-fast organisms.

DR. SCHEFF: No, they were not.

DR. ALEXANDER: In summary, it may be said that there appears to be little unanimity of opinion among the staff as to the diagnosis. Hodgkin's disease was considered the most likely diagnosis when the patient was in the hospital and is still favored by some. Others have expressed the opinion that the patient was suffering from tuberculosis or Boeck's sarcoid or possibly from both. We have apparently been unable to assemble conclusive evidence in favor of any one of these possibilities. We are forced, therefore, to ask the pathologists to enlighten us as to the correct diagnosis.

PATHOLOGIC DISCUSSION

DR. ROBERT A. MOORE: From the gross findings the diagnosis at the time of the autopsy was a granulomatous disease involving particularly the right lung, and to a lesser extent, the liver, the spleen and the porta-hepatic lymph nodes. The real problem, therefore, was to identify the nature of this granulomatous process. Examination of the microscopic sections was necessary to determine the diagnosis. Figure 3 shows a section of one of the nodules in the lung. The lesion is distinctly granulomatous; there is necrosis in the center and in some areas there is caseation. Surrounding some of the nodules fibrosis is seen and there is an occasional giant cell about the edge of the nodule. There are epithelioid cells with finely vacuolated cytoplasm in the periphery. Essentially normal pulmonary tissue lies adjacent to the nodule.

In Figure 4 another nodule is seen with greater magnification. There is necrosis in the center of a group of epithelioid cells; at the periphery, fibrosis is developing. There are numerous capillary vessels in the young proliferating fibrous tissue. An acid fast stain showed acid-fast bacilli at the center of the necrotic foci in the lungs and other organs.

Figure 5 is a section of the surrounding lung showing a mononuclear exudate in the alveoli and proliferation within the alveolar wall. In other words there was a tuberculous pneumonia about the granulomatous lesion in the right lung.

In Figure 6 a section of a tracheobronchial lymph node is seen; there is complete caseation of the central part of the lymph node with slight cellular infiltration in the capsule. This type of lesion in a tracheal-bronchial lymph node is seen in first-infection tuberculosis. In other words, there is massive caseation of the lymph node extending to the capsule with a sharp line of

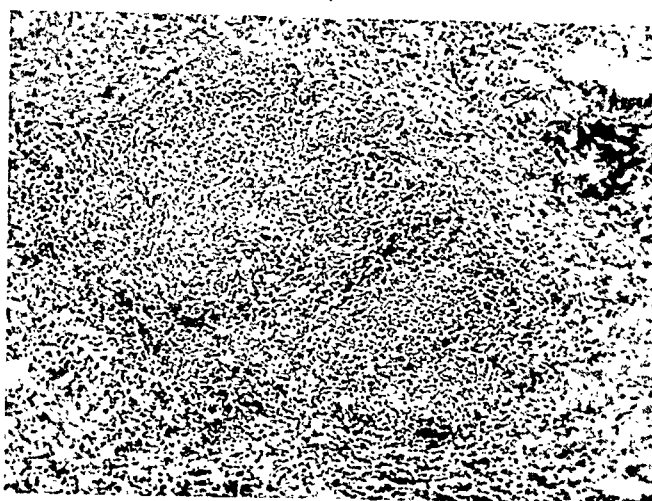


FIG. 3. (No. 46-1204). Microscopic section of a pulmonary nodule showing necrosis and caseation with peripheral fibrosis. $\times 47$.

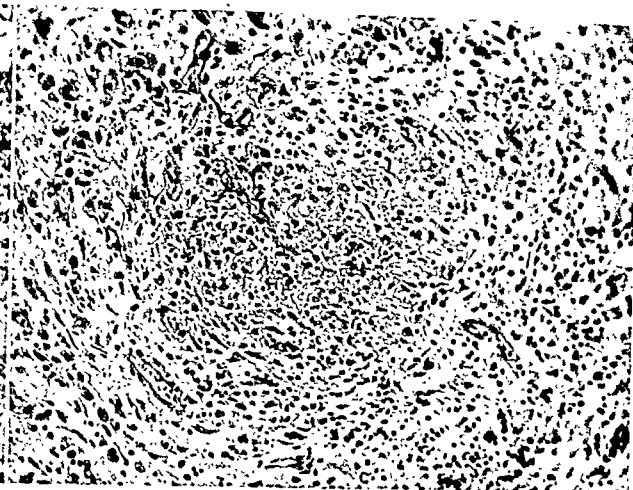


FIG. 4. (No. 46-1197). Microscopic section of a pulmonary nodule under higher magnification. Note the central necrosis and peripheral fibroblastic and capillary proliferation. $\times 97$.

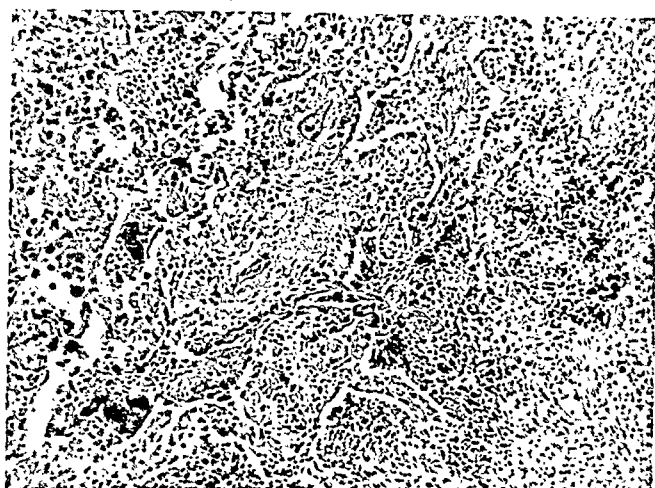


FIG. 5. (No. 46-1198). Microscopic section of an area in the right lung showing a mononuclear exudate. $\times 47$.



FIG. 6. (No. 46-1196). Microscopic section of a tracheobronchial lymph node. Note central caseation and the sharply demarcated fibrous tissue capsule. $\times 47$.

demarcation between the fibrous tissue of the capsule and the caseous lymphoid tissue.

Figure 7 pictures a section of the spleen showing a similar necrotic granulomatous lesion in the splenic pulp. Here, in contrast with the pulmonary lesions, there is practically no reaction about the focus of necrosis, no epithelioid cells and no fibrosis, but the necrotic area extends directly to join the splenic pulp. There were acid fast-bacilli in the necrotic nodules. Thus, in the lung, in the spleen and in the liver there was necrosis of tissue and the lesion was of the type described as necrotizing tuberculosis. The tubercles were necrotic rather than caseous. Under higher magnification the

character of the necrosis could be seen; numerous strands of fibrin permeated the necrotic areas. In caseous tuberculosis threads of fibrin are not seen.

Sections of the pericardium indicated that it was involved by the tuberculous process; so-called lymphocytic tubercles were identified in the pericardium.

In Figure 8, another variant of the reactions of tuberculosis is seen; the section is taken from one of the ulcers in the skin of the thorax. A blood vessel is shown; it is thickened in parts because of edema and because of cellular infiltration. Such a lesion with the marked intimal proliferation is representative of tuberculous granulation

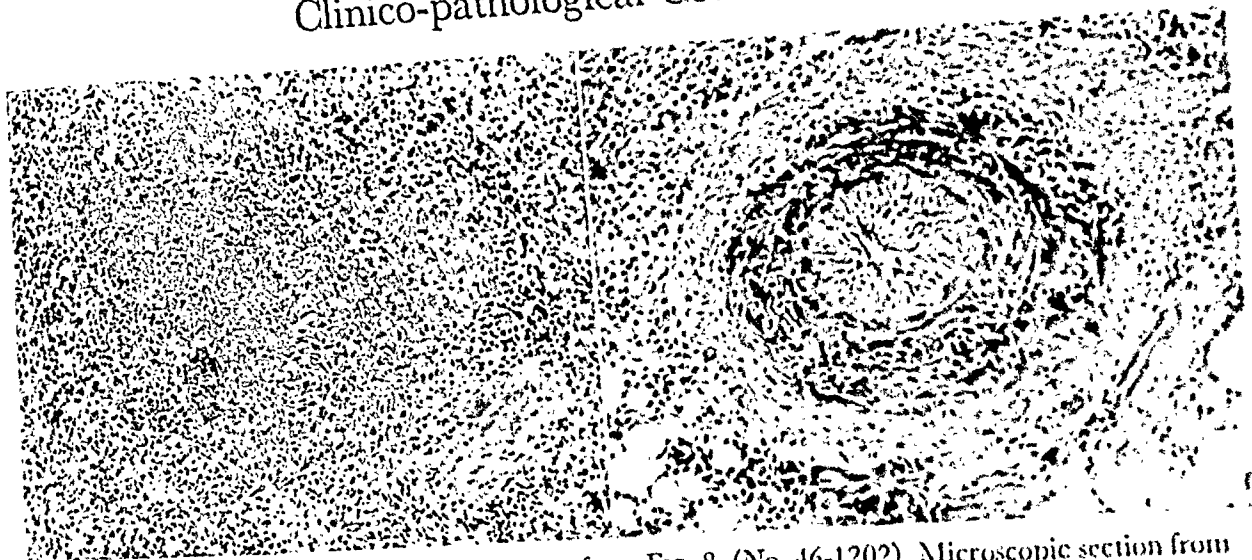


FIG. 7. (No. 46-1199). Microscopic section of nodule in spleen showing necrosis and absence of cellular reaction about the focus. $\times 47$.

FIG. 8. (No. 46-1202). Microscopic section from a skin lesion showing characteristic reaction of a blood vessel in tuberculosis.

tissue. Characteristically, it is seen in the meninges and may at times be the only histologic evidence on which the diagnosis of tuberculosis is based. The lesion is not frequently seen in other viscera.

The bone marrow showed hyperplasia, particularly of the red cell series, but there were no granulomatous lesions in the marrow; it is understandable, therefore, that no acid-fast bacilli were found in smears of the marrow. In the testis there was hemorrhage into the interstitial tissue and atrophy of the seminiferous tubules; the latter change occurs in patients suffering from chronic debilitating disease. The spermatogonia and the cells of the spermatogenic series were entirely absent; the centers of the seminiferous tubules were filled with cells of the Sertoli type, and the basement membrane was greatly thickened and appeared edematous.

It is apparent from the description, both gross and microscopic, that the patient had granulomatous lesions in which acid-fast bacilli were demonstrated and of which the histologic structure was consistent with a diagnosis of necrotizing tuberculosis. To reconstruct the exact clinical course of this patient is difficult. Apparently he had a first infection tuberculosis as evidenced by the calcified nodules in the *x-ray* film of the chest; he also had re-infection tuberculosis

as demonstrated at the autopsy by fibrous scars at both apices. About six months before entry, either the tuberculosis was re-activated from the fibrous scars or the patient acquired a new infection. The process went on for some time in reasonable equilibrium and the patient did not become critically ill until three to five weeks before his death. At that time the lesions took on another character; they became necrotizing in type, causing vascular spread and a rapidly fatal course.

There was no evidence in the sections of any additional disease such as sarcoidosis. All of the nodules that were observed were characteristic of tuberculosis.

Final Anatomical Diagnosis. Fibrous scars of the apices of the lungs; caseous and necrotizing tuberculosis of all lobes of the right lung; pleural effusion (right 1,500 cc., left 50 cc.); caseous and necrotizing tuberculosis of the tracheobronchial lymph nodes; necrotizing tubercles in the liver, porta-hepatic lymph nodes, spleen and right pleural surfaces; tuberculosis of skin with ulceration and secondary suppurative inflammation; localized areas of reddish discoloration of skin; desquamation of skin of trunk and extremities; "lymphoid tubercles" in the pleura-pericardium, and atrophy of the testis with focal hemorrhages.

Extensive Polycystic Disease of the Kidneys and Liver*

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POLYCYSTIC kidney disease has been extensively studied both in this country and abroad. It is reported to occur at autopsy approximately in the proportion of 1 to 500 cases. An exhaustive and excellent study of this condition was made by G. D. Oppenheimer in 1934,¹ and E. T. Bell² in 1935. Polycystic liver disease is less frequently encountered. A detailed study of this condition was made by L. Severi³ in 1937.

Polycystic disease is believed to be a congenital affection. Individuals afflicted with it usually develop gradually increasing renal insufficiency and die with the symptoms of uremia. Tetany has not been often mentioned as a complicating feature. The following case is of interest in this respect. It is also of interest because of the extensive involvement of the liver.

CASE REPORT

A forty-four year old housewife was admitted to the Lebanon Hospital to the service of Dr. David Greenberg on October 5, 1937, complaining of weakness, headache, vertigo, dragging sensation in the abdomen and nocturnal attacks of pain and spasm in the toes and fingers. The family history was essentially negative and outside of a herniorrhaphy four years ago, there were no previous illnesses. She was married and had four children; all four pregnancies and deliveries were normal and uneventful. There was amenorrhea for the past three months.

The patient was apparently well until about six months prior to admission when she began to experience the gradual onset of weakness, headache and dizziness. Three months prior

to admission she began to complain of being awakened at night with severe attacks of pain, spasm and cramps in the toes and fingers. She also felt a dragging heavy sensation in the abdomen, and complained of pyrosis, eructations, habitual constipation and "palpitation of the heart" with attacks of precordial pain. She lost no weight. There were occasional bouts of jaundice lasting from one to three days. Physical examination revealed slight jaundice, marked venous pulsations in the neck, systolic murmur over the base, blood pressure 118/80, a markedly enlarged liver which reached to the level of the umbilicus; the edge was hard and nodular but not tender; the spleen was enlarged, its edge was smooth and not tender.

Roentgen examination of the gastrointestinal tract disclosed an irregularity in the stomach which was interpreted as an organic lesion in the pars media of the stomach; x-ray of the chest was negative; x-ray of the genitourinary tract showed a large and ptosed right kidney; the left renal outline was visualized. Intravenous pyelogram revealed filling of the pelvis and calyces of the left kidney but there was an absence of the opaque media in the pelvis and calyces of the right kidney. During cystoscopy no urine could be obtained from the left side and the dye did not appear from either orifice in half an hour. The total phenolsulphonthalein excretion was 2 per cent. The specific gravity of the urine was fixed between 1.008 and 1.012 with an average daily output of 1,200 cc. It contained 1 plus albumin but no sugar. Microscopic examination showed occasional white and red blood cells. Blood count: red blood cells; 3,200,000; white blood cells 5,800; polymorphonuclears 72 per cent; lymphocytes 22 per cent; mononuclears 1 per cent; basophils 1 per cent; platelet count, coagulation and bleeding

* From the Laboratory of Lebanon Hospital, New York City, N. Y.

Polycystic Disease—Lefkovits

time were normal. The hemoglobin was 55 per cent (Sahli). Gastric analysis showed no free hydrochloric acid the total acidity being 10; there was no free hydrochloric acid after histamine injection. The basal metabolic rate was 0; stools were negative for occult blood. Blood chemistry findings are shown in Table 1. Temperature and pulse were always normal. Because of the x-ray findings in the stomach a diagnostic laparotomy was performed. The stomach was normal but the liver was found to be cystic. Biopsy of the liver showed congenital polycystic disease of the liver.

TABLE 1

	1st Admission	2nd Admission	3rd Admission
Non-protein nitrogen	120	204-162	255-300
Urea nitrogen	98	90	
Serum protein	5.2	8.5	6.7
Albumin	2.4	3.8	3.6
Globulin	2.8	4.7	3.1
A/G ratio86	.81	1.2
Icteric index	6	7	
Total cholesterol	155	194
Cholesterol esters	69	79
Phosphorus	9.5		
Phosphatase	2.1 (Bodansky)		
Calcium	8.4		

The postoperative course was uneventful and the patient was discharged with some improvement on November 23, 1937. She felt fairly well and had no complaints until May, 1938, when her symptoms of heartburn, vomiting, constipation and dizziness recurred. She was re-admitted to the hospital on June 4, 1938. At this time blood chemistry showed increased retention of nitrogenous waste products. (Table 1.) There was urobilin in the urine. The patient developed an infectious dermatitis during her stay in the hospital which was treated symptomatically. She showed some improvement; the non-protein nitrogen fell to 162 mg. per cent, and she was discharged on June 29, 1938.

She was re-admitted on September 22, 1938, with the symptoms of moderate uremia. She now was emaciated, the skin was bronzed and she appeared acutely ill. The liver edge was nodular and hard; its edge was felt at the level of the umbilicus. Both kidneys were palpable;

there was no ascites. On admission the hemoglobin was 45 per cent (Sahli); red blood cells 3,160,000; white blood cells 11,000; polymorphonuclears 80 per cent; lymphocytes 12 per cent; mononuclears 6 per cent; non-segmented polymorphonuclears 2 per cent. There was achromia, aniso- and poikilocytosis. The specific gravity of the urine was fixed between 1006 and 1008, and it contained 2 plus albumin and pus clumps. Blood chemistry showed increased retention of nitrogenous waste products. (Table 1.) The total non-protein nitrogen rose to 300 mg. per cent on September 28, 1938. The patient expired on October 6, 1938.

Autopsy: Only the kidneys and liver are described. Both kidneys were enlarged; their vertical diameters measured approximately 25 cm. Their surfaces were markedly irregular and were studded with variously sized cysts. The capsule stripped with moderate difficulty. (Figs. 1 and 2.) On section, the cut surfaces appeared irregularly honey-combed by the cross section of numerous variously sized cysts separated in most places by narrow strips of parenchyma or, in many places, only by their opposing walls. Most of the cysts contained a straw-colored serous fluid; some of the cysts contained a sanguineous turbid fluid, while still others were filled with a gelatinous homogeneous mass. The pelves were somewhat dilated, the ureters were patent. The microscopic appearance of the organ was that of variously sized cysts, many of which were markedly dilated. The smaller of these cysts were lined by low cuboidal epithelium which resembled that of collecting tubules, while the larger cysts were lined by a very markedly flattened epithelium. The cysts were filled with a pale pink staining amorphous material in which were seen red blood cells and cellular debris; other cysts, in addition, contained a purulent exudate. Among the cysts there were seen considerable areas of functioning kidney parenchyma. In these areas moderate numbers of fairly well preserved glomeruli were found which showed a mild degree of congestion, a moderately increased cellularity of the epithelium with beginning hyaline changes and edema. The tubules were irregular and most of them markedly dilated. Their epithelial walls were flattened and showed moderate to marked degrees of degenerative



FIG. 1. External surface of polycystic kidney. Note the closely packed cysts which vary in shape, size and depth.



FIG. 2. Cross section of polycystic kidney. Note the almost complete replacement of kidney tissue by the various sized cysts.



FIG. 3. Cross section of polycystic liver. Note the close resemblance to the cross section of the kidney.

changes. The interstitial connective tissue was markedly increased and, in most places, it was infiltrated by mononuclear cells. There was also a moderate degree of congestion present throughout. The blood vessels showed only minimal sclerotic changes; most of them appeared normal.

The liver weighed 4,200 Gm. and extended to about one finger above the umbilicus. The surfaces were irregularly nodular with cysts which varied in size from a few millimeters to 5 to 10 cm. in diameter. The diaphragmatic portion of the right lobe was the only part of the liver which was found to be relatively free of cysts. On section (Fig. 3) the cut surfaces resembled those of the kidneys and were also irregularly honey-combed by the cross sections of cysts most of which contained a clear serous fluid, while others contained a turbid brown fluid or a gelatinous homogeneous mass. In the

relatively uninvolved portions, the liver parenchyma presented a fairly normal appearance. The gallbladder and biliary tracts appeared normal. Microscopically, sections through the uninvolved portions showed normal liver architecture; there was a moderate degree of edema and the cytoplasm of the liver cells showed granular degeneration; the nuclei, however, were fairly well preserved. The portal fields seemed to be less prominent than seen normally. Sections taken from the cystic area showed numerous variously sized cystic cavities. The smaller of these were lined by low cuboidal epithelium resembling that of the bile ducts, while the larger cysts were lined by a markedly flattened epithelium. The cysts contained pale pink amorphous substance; there was no bile pigment seen in them. Some of these cysts were filled with a polymorphonuclear exudate and there was a similar infiltration in the adjacent

liver parenchyma surrounding them. The larger cysts were surrounded by a thickened fibrous wall. The liver tissue in between these cystic areas showed all grades of degenerative changes.

COMMENT

This case presented several noteworthy features. It is interesting to note that with such extensive involvement of both kidneys and liver this patient was able to lead a fairly normal existence up to a few months prior to her death. This ability to carry on in spite of these serious handicaps seems to depend upon two factors: First, the uninvolved portions of the kidneys and liver parenchyma undergo hypertrophy and partially compensate for the tissue destroyed by the cysts. This compensatory mechanism is especially marked in youth and early adult life. With advancing age, however, this ability is gradually decreased; the cysts on the other hand, continue to enlarge, gradually replacing the persistent islands of functioning tissue. As a result, the destruction of the latter goes on more rapidly than it can be replaced by compensatory hypertrophy and the patient progresses toward renal or liver insufficiency and death. The second factor in maintaining a normal existence is the ability of the organism to adjust itself and to acquire an increased tolerance to the accumulation of waste products in the blood. Another interesting feature of this case was the low blood pressure. Throughout the patient's stay in the hospital during the three admissions the blood pressure never rose above 118/80. This may be explained by the fact that the vessels of the kidney showed little or no sclerotic changes. It is now generally recognized that hypertension occurs in cases in which there is serious interference with the blood supply of the kidneys as shown by the well known experiments of Goldblatt⁴ who was able to produce hypertension in dogs by partially clamping the renal arteries.

The third feature of interest was the development of tetany. Symptoms of tetany have been observed to occur in cases of chronic nephritis. This is usually explained by the fact that due to the decreased ability of the kidney to excrete inorganic salts there is an accumulation of inorganic phosphates in the blood; with this the calcium is decreased since it has been shown that the relationship between these two elements tends to be reciprocal. The consequent development of hypocalcemia and the decrease in the serum calcium/phosphorus ratio is believed to play a significant rôle in the precipitation of clinical symptoms of tetany.⁵

The irregularity in the body of the stomach as revealed by x-ray was probably produced by pressure of the encroaching cysts of the left lobe of the liver upon the walls of the stomach. This was erroneously interpreted as a gastric neoplasm.

SUMMARY

1. A case of extensive polycystic disease of the kidneys and liver is reported in a forty-four-year old housewife.
2. There was no hypertension in spite of the extensive involvement of both kidneys.
3. The symptoms of tetany in this case were attributed to the increase of inorganic phosphates in the blood with a concomitant development of hypocalcemia and decrease in the serum Ca/P ratio.

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Mycotic Lung Infection*

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LUNG "cysts" are liable to infection. A case seeming to illustrate this is herein reported:

CASE REPORT

Mr. C. G. was admitted, at the age of fifty-five, to the Mount Morris Tuberculosis Hospital in May, 1937. He had been a glass cutter all his

the second rib and sixth dorsal spine. Breath sounds were roughened and crackling râles were audible above the clavicle and the fifth dorsal spine. On the left, an occasional râle was heard over the apex. X-ray films confirmed the clinic films. The patient was raising 3 to 4 ounces of odorless, mucopurulent sputum. A blood study revealed nothing except leucocytosis and eosino-

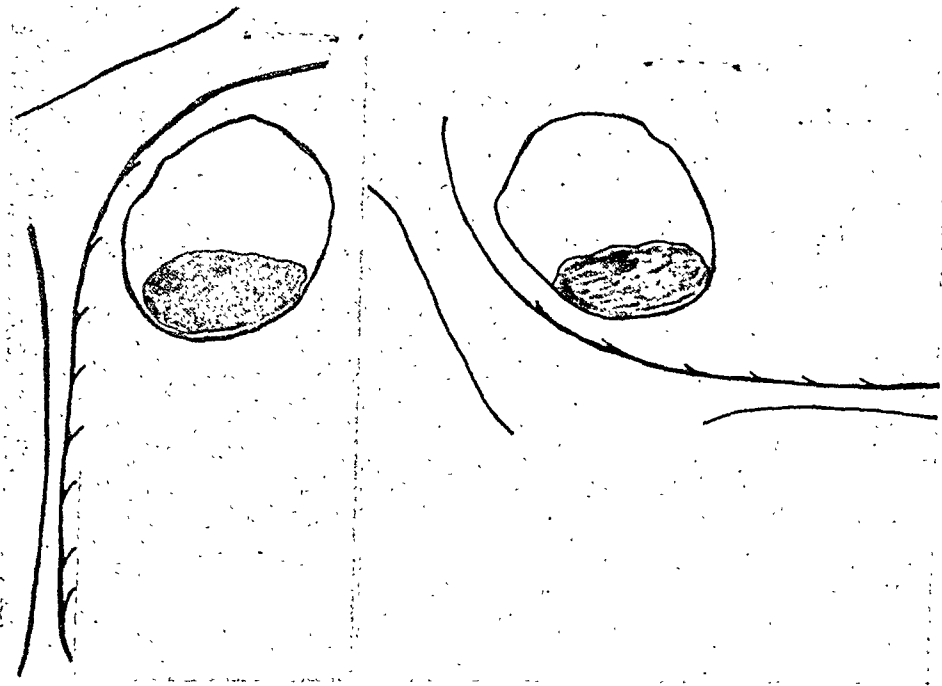


FIG. 1.

FIG. 2.

FIGS. 1 and 2. Sketches of the right apex in the erect anteroposterior (Fig. 1) and right lateral recumbent (Fig. 2) illustrating diagrammatically movement of the intracavitary mass with change in position.

life. The past history was non-contributory, except that he had "pleurisy" every year for the past ten years. In February, 1937, he contracted a cold, followed by a cough which became productive, and increasing weakness. X-ray in an itinerant clinic revealed a cavity at the right apex, with light infiltration at the left apex and he was admitted to this hospital.

Significant findings were limited to the chest, where on the right side there was dullness to

philia of 6 per cent, and sputum studies failed to reveal tubercle bacilli, fungi or Vincent's organisms. His temperature was subfebrile. The cough was paroxysmal and violent, especially when the patient was in the recumbent position. Bronchoscopy revealed inflammation of the right upper lobe bronchus.

X-ray films taken in January, 1938, in various positions revealed that there was a loose body in the cavity which shifted with change of

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position. This body was roughly circular, about 3 cm. in diameter, and could be seen to gravitate freely in a cavity three times as large. (Figs. 1 and 2.) On February 16, 1938, operation by a posterior approach disclosed an irregular cavity containing inspissated material having a mousy odor. This cavity had several bronchial communications. After adequate drainage, myoplasty was done to close the cavity and obliterate the bronchocutaneous fistulas. The patient was discharged from the hospital February 11, 1939, cured. Eosinophilia on discharge was 3 per cent.

A section of the thick cavity wall revealed "a zone of fibrotic tissue with marked necrosis of the inner layer. All layers are infiltrated with eosinophils." Neither yeast, molds, fungi nor tubercle bacilli were seen.

The cavity contents were shown by microscopic examination to be mycotic material of the aspergillus group. Attempts were made to identify the organism more definitely but all cultures failed to grow.

Follow-up on November 7, 1944, revealed that the patient has been working as a glass cutter and is apparently well.

COMMENTS

The occupational history of glass cutting, involving the use of carborundum and pulverized sand, for forty years, confused the picture, as did the presence of some infiltration at the left apex, interpreted as being tuberculosis. The exact mechanism involved in the condition described is obscure. It is suggested that there was a lung cyst or emphysematous bleb at the right apex. This sustained an aspergillus infection, which then died, leaving a thick-walled cavity containing a mobile, putty-like mass of dead organisms. This mass sometimes acted as a ball-valve over the bronchial fistulas causing the severe paroxysmal cough.

Venous Catheterization

ADVANCES in medicine depend on the development of new methods. It is easy to think of things that one would like to know. It is more difficult to outline a problem for which methodology to give the needed information is available. Interest in cardiovascular research has been greatly stimulated by the demonstration of South American investigator¹ and by the group at Bellevue Hospital that a radio-paque catheter can be safely introduced into the venous system through an incision in a superficial vein.^{2,3} Once in the vein, the catheter may be guided under the fluoroscope into the jugular vein, the right atrium, the right ventricle or the pulmonary artery. It may be passed down through the right atrium into the inferior vena cava and on out into the hepatic or renal veins. In patients with atrial septal defect, the catheter may enter the left side of the heart. In patients with a ventricular septal defect, the catheter may be passed into the aorta.

This method has had immediate clinical application in the diagnosis of certain types of heart disease. High right ventricular pressure is present in patients with cor pulmonale.⁴ The presence of certain types of shunts can be demonstrated by study of the oxygen content of samples of blood drawn from different chambers of the

heart.^{5,6} These diagnostic methods are of great interest because of the recent advances in cardiac surgery.

Venous catheterization has opened a wide field of investigation in the field of cardiac dynamics. The lesser circulation can now be studied and many questions concerning the control of blood flow through the lungs will be answered in the near future. The data obtained on the relations between atrial pressure and ventricular filling will lead to a better understanding of the factors controlling the cardiac output.

A method for measuring the hepatic blood flow using the technic of hepatic vein catheterization has recently been described.⁷ Studies on the metabolism of the kidney are now possible as methods are available for obtaining both the renal blood flow and the renal arteriovenous oxygen difference.⁸

At least 1,500 persons have been subjected to this procedure in the last four years. Thrombosis at the site of the incision in the antecubital vein occurs occasionally. There have been no serious complications. It seems safe to predict that venous catheterization will become an accepted technic in many hospitals.

EUGENE A. STEAD, JR., M.D.

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Book Review

THIS small, inexpensive volume,* "A Primer for Diabetic Patients," contains a surprising amount of practical information for the diabetic patient which should lead to his informed cooperation in management.

The first five chapters contain brief simple discussions of diabetes, the urine tests, the insulins, the complications of diabetes and their remedies. The last four chapters, comprising more than half the book, are devoted to foods and diets and are sufficiently detailed to permit anyone of average intelligence to plan palatable menus of known composition. Questions at the end of each chapter are designed to emphasize the important points covered.

* A PRIMER FOR DIABETIC PATIENTS. By Russell M. Wilder, M.D., PH.D., F.A.C.P. Eighth edition reset. Cloth. Pp. 192 with 8 illustrations. Philadelphia, 1946. W. B. Saunders Company. Price \$1.75.

While the value of the "Primer" is undisputed, and its popularity attested to by the number of editions published, certain minor criticisms may perhaps be ventured. The insistence that in general not more than twenty units of protamine zinc insulin should be used in one day seems a trifle conservative. Perhaps more stress is placed on weighing foods and learning their substitution value in a standard diet than teaching their composition and actual caloric equivalents. The height-weight-age tables at the back of the book are in type so small as to be difficult to read.

However, these are hardly serious objections. Otherwise, the clarity and detail of the presentation, the excellence of the typography and the handy pocket-sized format make the "Primer" prescribed reading for every diabetic.

F. K. H.

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The American Journal of Medicine

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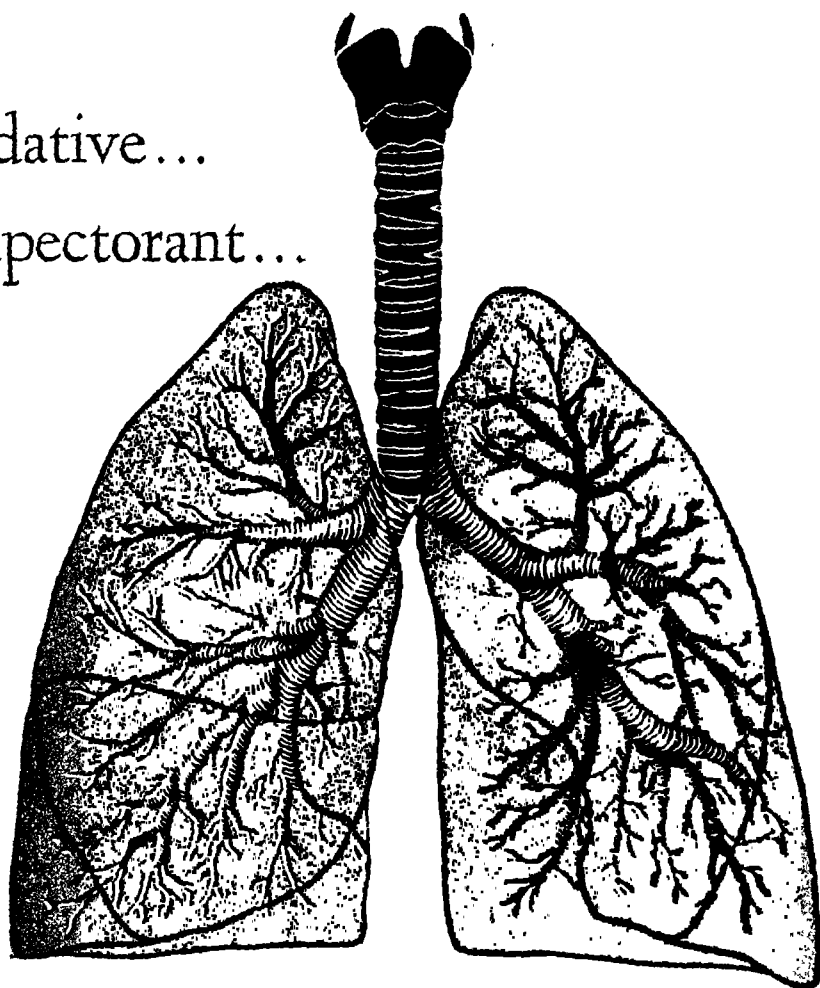
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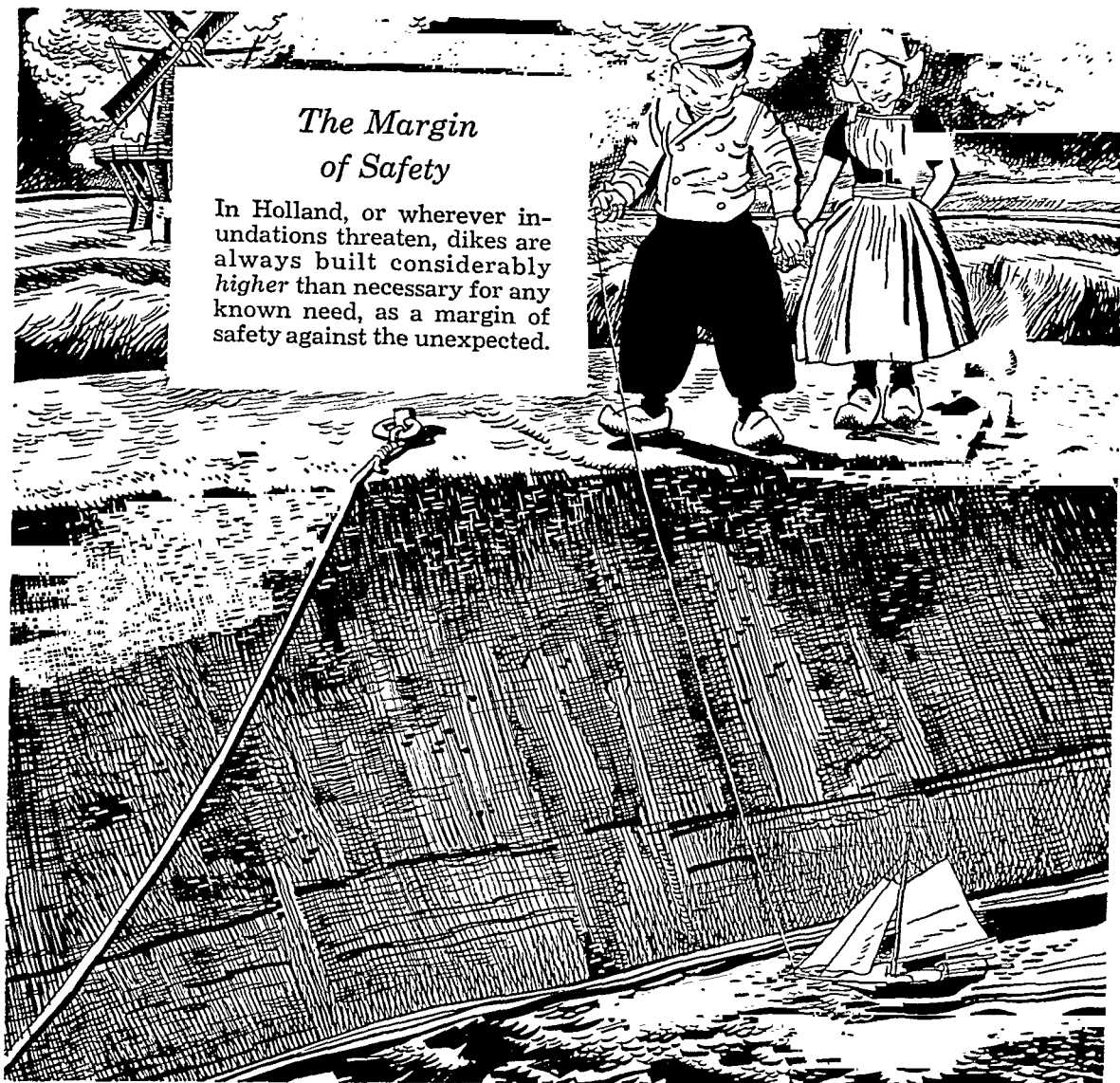


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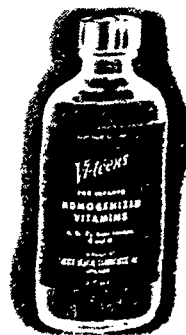
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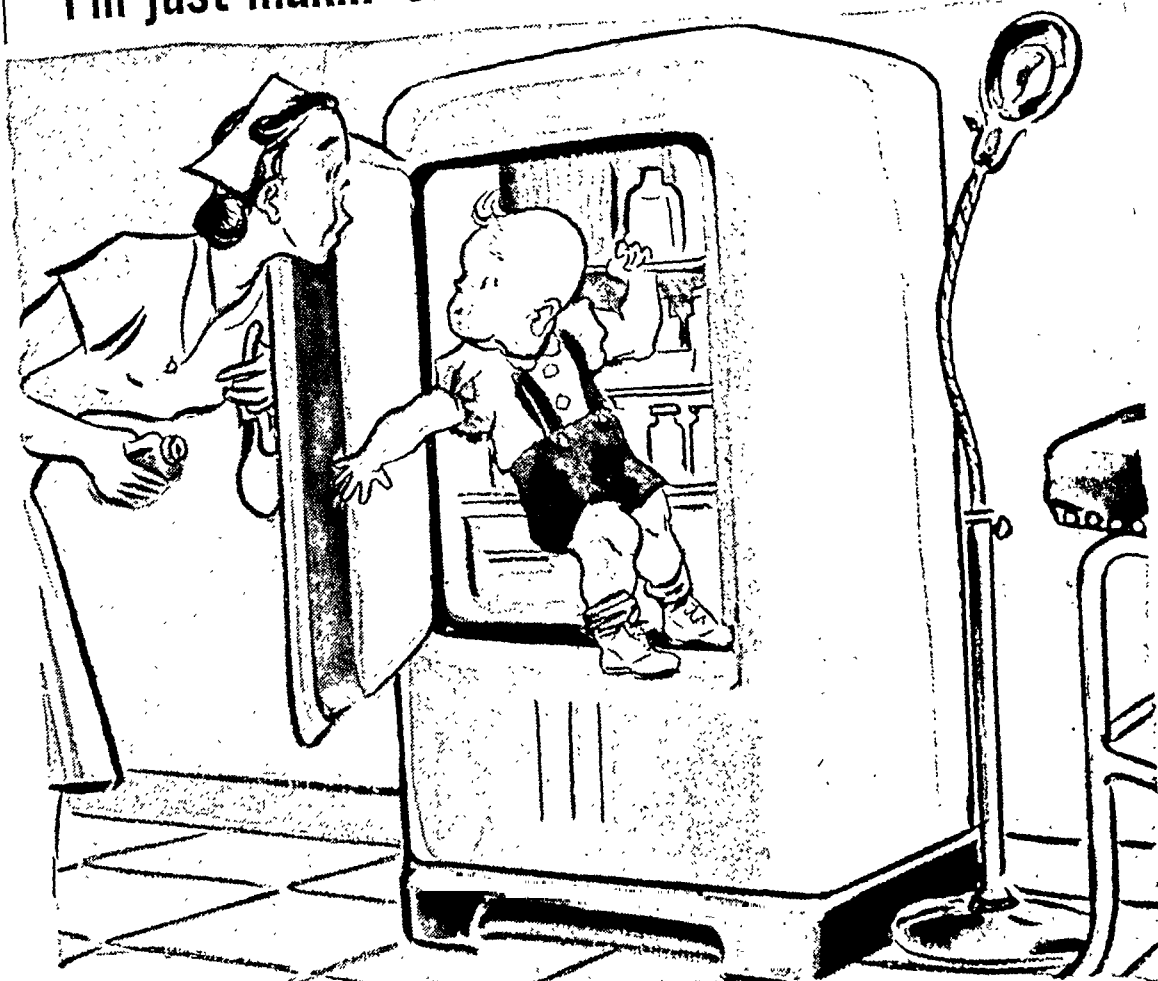
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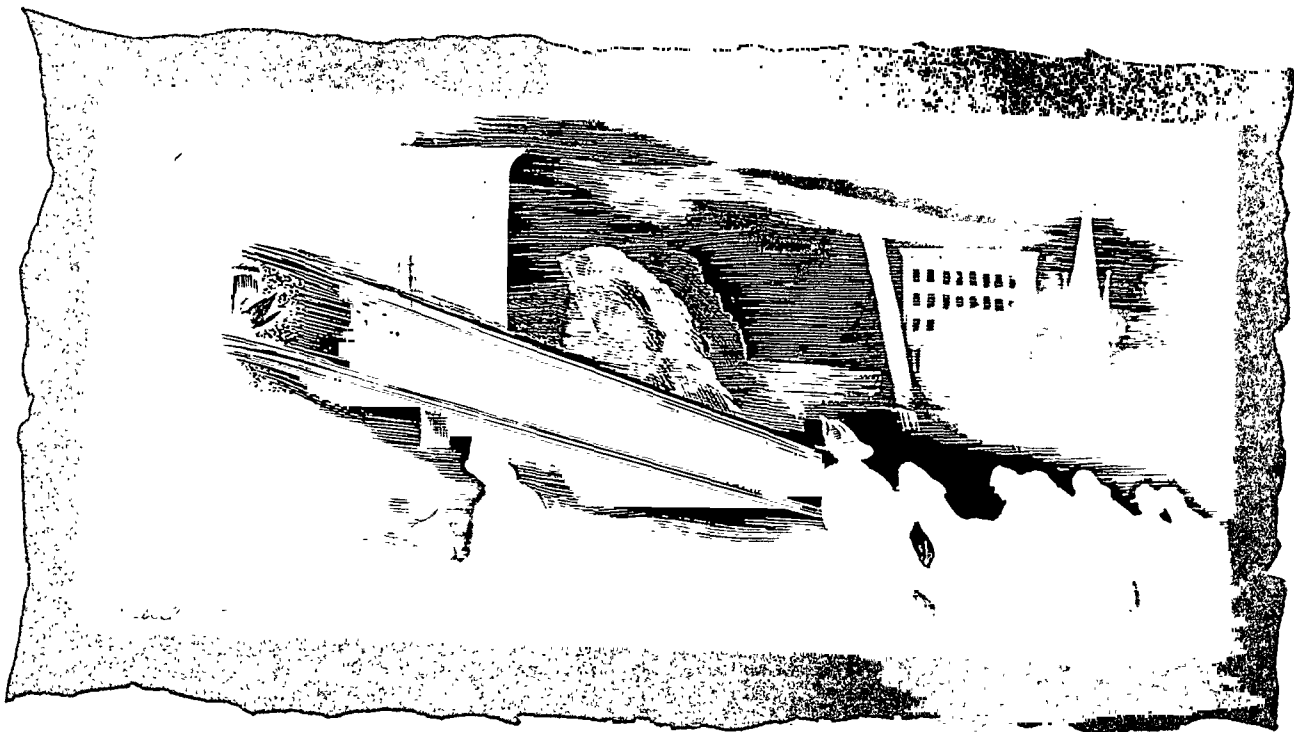
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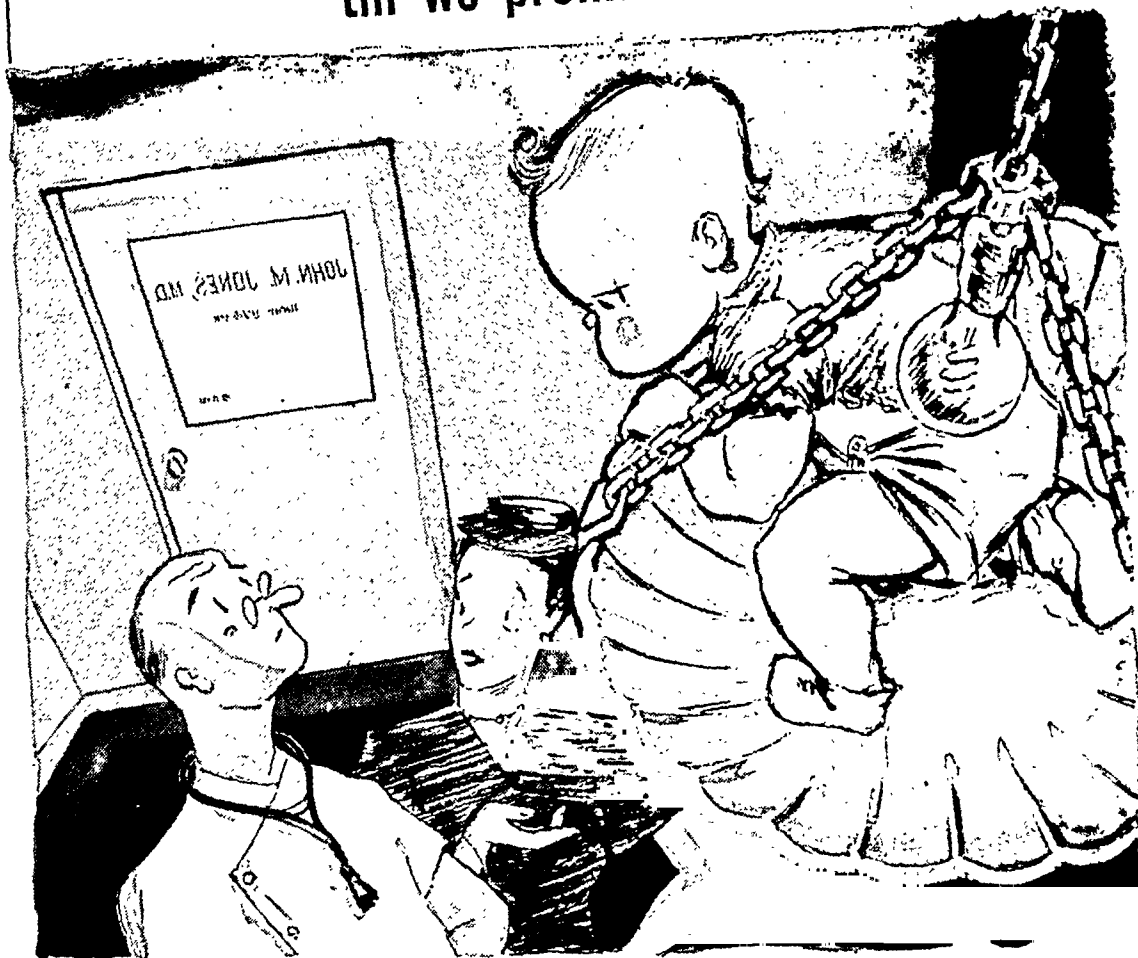
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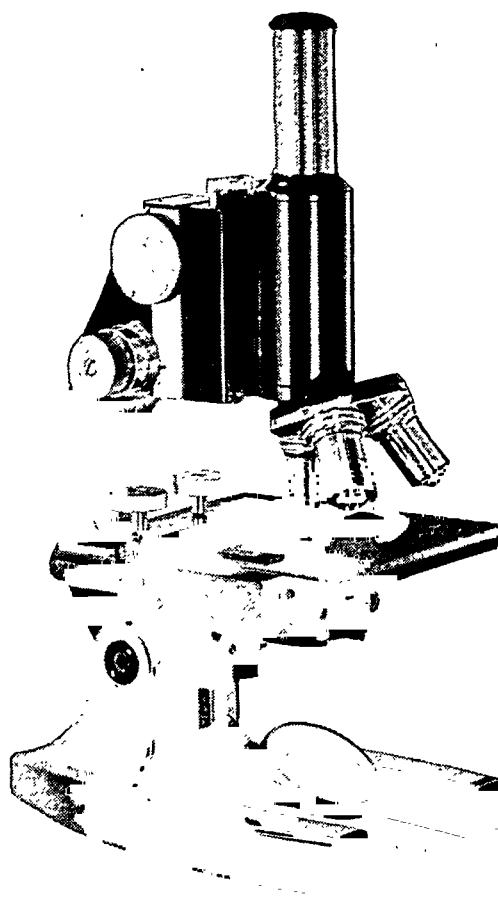
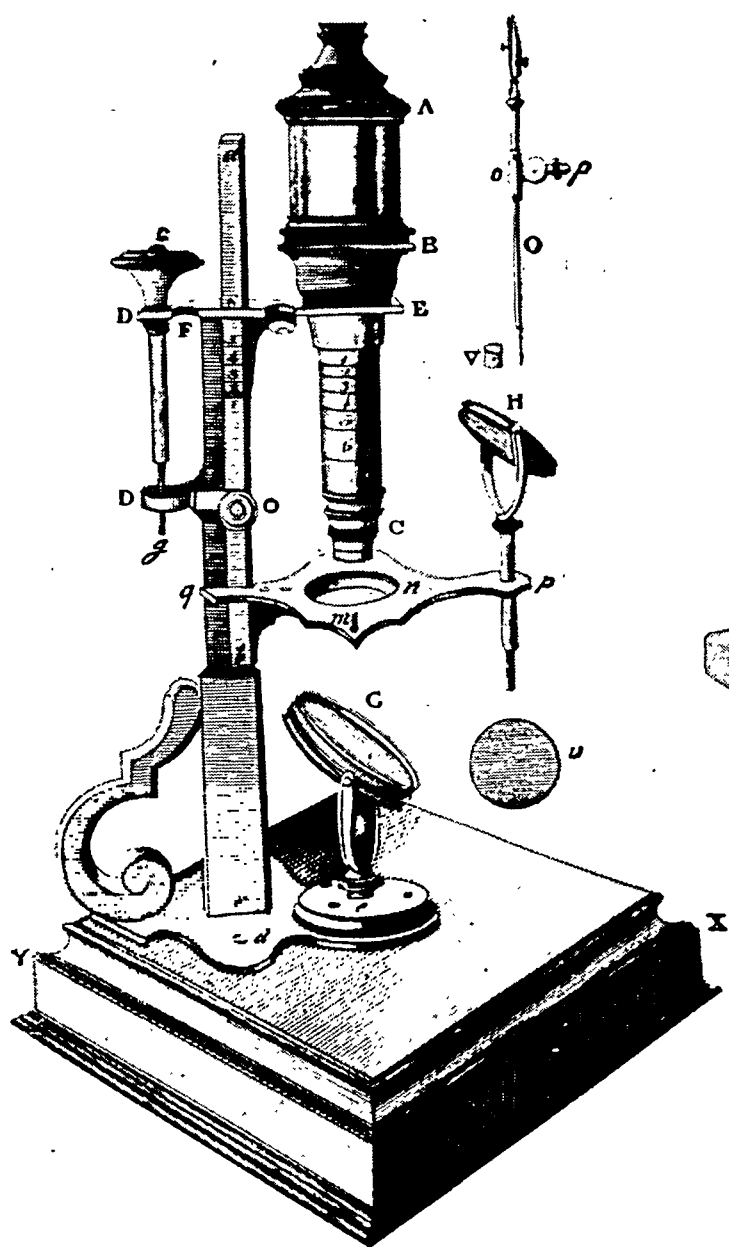
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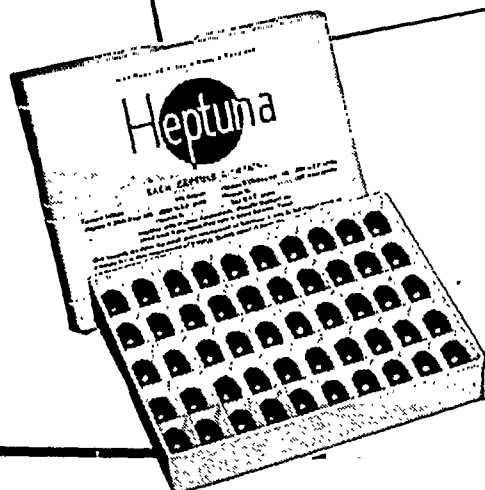
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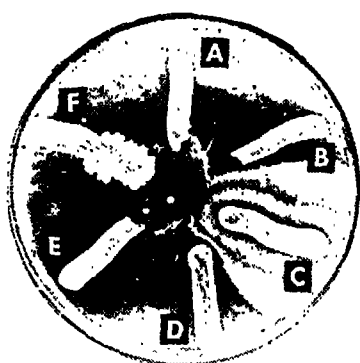
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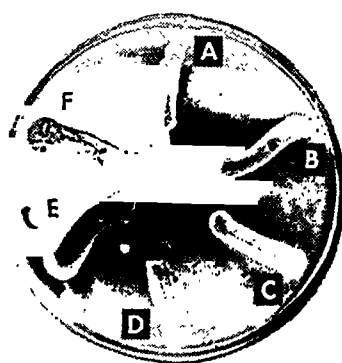
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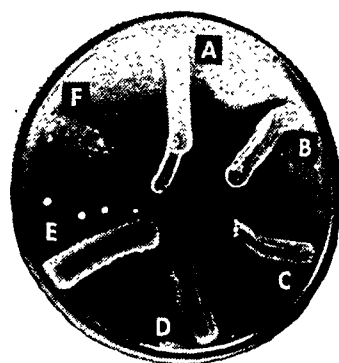
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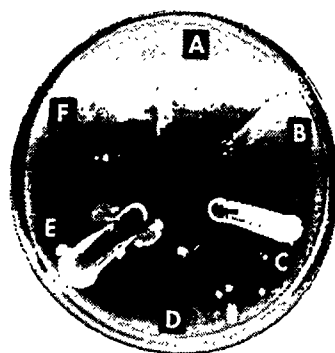
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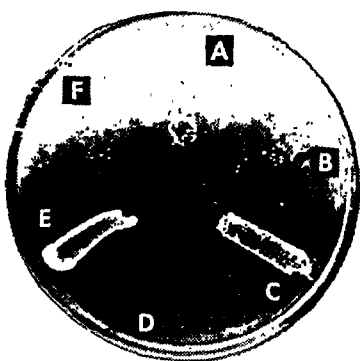
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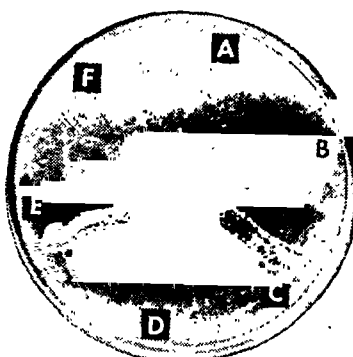
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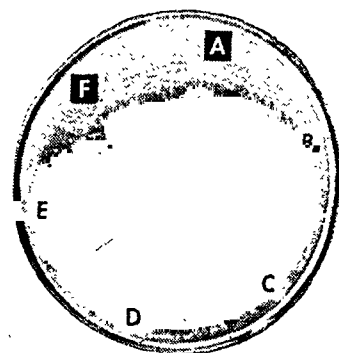
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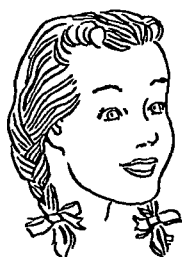
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The Anticonvulsant Properties of Tridione*

Laboratory and Clinical Investigations

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SALT LAKE CITY, UTAH

TRIDIONE, 3,5,5-trimethyloxazolidine-2, 4-dione, has recently been made available to physicians as a specific symptomatic therapy for petit mal epilepsy, and has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in New and Nonofficial Remedies. The drug was synthesized by Spielman³¹ and initially studied and reported as an analgesic agent.^{26,28} Its pharmacological and anticonvulsant properties were described by Richards and Everett^{8,26,27,28} and by us.^{13,14,15,17,18,34,35,38,42,43} The earliest observations on the specificity of Tridione in petit mal were made by Perlstein,²⁹ and the most extensive clinical studies to date are those of Lennox.^{21,22} The field of usefulness of Tridione has also been extended to psychomotor epilepsy.^{5,24,29} Available evidence indicates that Tridione offers no advantage in the treatment of grand mal.^{22,24,27,36} Preliminary observations have been made on its use in tetanus and status epilepticus,^{7,24,27,29,35} in athetoses and in behavior disturbances in children.^{24,29}

The following report is concerned with

the laboratory analysis of Tridione* in comparison with other anticonvulsant drugs, and with the clinical results obtained in a selected group of patients with slow wave EEG dysrhythmias, particular attention being paid to the EEG criteria for the use of Tridione alone or in combination with other agents. This study is part of a program concerned with properties of experimental and clinical convulsive disorders and their therapy. Tridione has received particular attention because elucidation of its mechanism of action in petit mal can yield considerable information on the nature of this disorder. New experimental methods reported here for analysis of anticonvulsant drugs may provide the basis for the discovery of agents which have higher therapeutic indices or greater specificity of action.

TECHNICS AND MATERIAL

I. LABORATORY STUDIES. The following six laboratory indices were used for the analysis of Tridione and its comparison with

* Generously supplied by Dr. R. K. Richards, Abbott Laboratories, North Chicago, Illinois.

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other agents. The first two are commonly accepted laboratory tests for the detection and assay of anticonvulsant drugs. The remaining four technics were devised in our laboratory to provide the basis for a more adequate comparison of such agents.

1. *Prevention of Metrazol Convulsions.* A standard convulsant dose (CD_{95}) of metrazol was determined for populations of mice and rats, and the convulsant dose of metrazol was established in individual cats, rabbits and monkeys. The protective potencies of Tridione and other anticonvulsant drugs were then ascertained.

2. *Elevation of Normal Electroshock Seizure Threshold.* Rats, rabbits, cats and monkeys were used. In most experiments, 60-cycle alternating current (Offner electroshock apparatus) and Spiegel corneal electrodes³⁰ were employed. Threshold current for fixed duration of stimulus (usually 0.2 sec.) was determined in each individual animal which then served as its own control for the subsequent study of anticonvulsant drugs.

3. *Elevation of Electroshock Threshold in Hydrated Animals.* The effect of Tridione and other anticonvulsants was studied in rats in which the electroshock threshold had been lowered by brain cell hydration resulting from extracellular electrolyte loss. The details of the procedure and the value of the technic as a screening device for anticonvulsant drugs have been described elsewhere.³⁴

4. *Modification of the Pattern of Maximal Electroshock Convulsions.* In rats, rabbits and cats the pattern of the seizure elicited by electroshock current intensities several times the threshold was analyzed. The effects of Tridione and other agents on individual components of this pattern were then studied. The details of the technic and its value for the laboratory detection of anticonvulsant drugs have been presented elsewhere.⁴³

5. *Modification of Non-convulsive EEG Dis-*

charges Induced by Cortical Stimulation. Rabbits were employed for these experiments. Aseptically implanted epidural electrodes were used for both stimulation and recording. Single condenser shocks were applied to one cerebral hemisphere while records were taken from the other. Thresholds were determined both for contralateral movement and for the various components of the EEG discharge. The effects of Tridione and other drugs on the threshold for and character of these cortically induced discharges were then determined. The details of this technic have been briefly reported.^{37,41}

6. *Prevention of Metrazol-induced Petit Mal-like Cerebral Dysrhythmias.* Rabbits with implanted epidural electrodes were used. The amount of metrazol, given either subcutaneously or by slow intravenous infusion, necessary to produce non-convulsive slow wave EEG dysrhythmia was determined both before and after administration of Tridione and other anticonvulsants. Details of the method have been described elsewhere.³⁸

II. CLINICAL STUDIES. Eleven patients with clinical histories of seizures and slow wave EEG dysrhythmias were placed on Tridione therapy and followed carefully for a period of six months or longer. Special attention was paid to seizure incidence and character, Tridione toxicity, effect of withdrawal, influence of the drug and its withdrawal on the EEG, and efficacy of combined drug treatment.

RESULTS

I. ANTICONVULSANT EFFECTS IN ANIMALS

1. *Prevention of Metrazol Convulsions.* In previous reports^{13,14,15,17,18,33} we have commented on the remarkable pharmacological antagonism between Tridione and metrazol. The quantitative features of this antagonism may be briefly summarized here.

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In all species tested (mice, rats, rabbits, cats, monkeys), a dose of Tridione smaller than that required to cause obvious neurological depression is capable of preventing completely all central excitatory effects of a dose of metrazol convulsant in 95 per cent of control animals (CD). Doses of Tridione causing minimal central depression are capable of protecting against approximately two CD'S. When still larger doses of Tridione are employed, several multiples of the CD of metrazol may be injected without evidence of central effects, the quantitative relationship being as follows (rats, rabbits, cats): Protection is afforded against approximately seven CD's of metrazol by each Gm. of Tridione per kg. of body weight. To emphasize the magnitude of this protection, it may be observed that barbiturates in equivalent neurological doses provide only approximately one-half this degree of protection. In single doses, diphenylhydantoin is ineffective against metrazol.^{12,16} We have also found that Tridione affords protection against picrotoxin, strychnine, and Coramine (mice, rats, cats), but the antagonism against these convulsants is not as great as that against metrazol.

Cats and rabbits were given equally depressant doses of phenobarbital and Tridione. Their neurological status and EEG's were then continuously examined during and subsequent to injection of metrazol. The Tridione-treated animals could be restored to normal by metrazol, but the phenobarbital-treated animals could not be similarly restored by any amount of metrazol up to and including that producing seizures.

The duration of action of single large doses of Tridione was determined in rats, rabbits, cats and monkeys. Protection against metrazol persisted for more than seventy-two hours. It was found that 30 per cent of the initial protection remained at twenty-

four hours (rats, rabbits). The persistence of Tridione action is longer than that of phenobarbital.

2. *Elevation of Normal Electroshock Seizure Threshold.* Monkeys, rabbits, cats and rats were employed for this standard laboratory test. In Table 1 are presented typical data obtained in rats. Tridione and phenobarbital contrast sharply with diphenylhydantoin in that the latter is not able to elevate significantly the normal electroshock threshold. Tridione appears to be somewhat more effective than phenobarbital with respect to this index. The results obtained in monkeys, cats and rabbits paralleled those for rats.

TABLE I
EFFECT OF ANTI-EPILEPTIC DRUGS ON NORMAL
THRESHOLD FOR ELECTROSHOCK SEIZURES
IN RATS

Drug	No. of Rats	Dose Mg./Kg. i.p.	Electroshock Threshold* in m.a. (Mean \pm S.E.)		Per Cent Increase in Threshold (Mean \pm S.E.)
			Initial Control	Threshold after Drug	
Controls.....	159	...	28 \pm 0.29	36 \pm 1.71	28.6 \pm 4.08
Tridione.....	12	400	28 \pm 1.07	38 \pm 1.58	20.6 \pm 3.81
Phenobarbital.....	15	45	31 \pm 1.61	30 \pm 2.24	1.7 \pm 2.7
Diphenylhydantoin...	10	60	30 \pm 2.60		

* 0.2 sec. stimulus duration.

It has been our consistent experience that anticonvulsant drugs administered in non-depressant doses either do not elevate the normal electroshock threshold (diphenylhydantoin) or do so only to a limited degree (Tridione, phenobarbital).^{13-18, 33, 34, 40, 43} In no species has it been possible to demonstrate that diphenylhydantoin significantly elevates the threshold for electroshock seizures. This has been found equally true both with 60-cycle alternating current stimulation of brief (0.2 sec.) or long (10 sec.) duration, and with the interrupted direct current method originally described by Putnam and Merritt.²⁵ Although the

character of the seizures could be modified by diphenylhydantoin, EEG evidence of convulsive discharge and overt evidence of post-ictal depression persisted well beyond the period of stimulation. With the long periods of stimulation customarily used by other investigators, we have consistently found that animals treated with diphenylhydantoin nevertheless exhibit overt seizures during the stimulation period whenever the control electroshock threshold has been exceeded. The effect of the drug is to decrease the total duration of the convulsion during the period of prolonged stimulation rather than to elevate the seizure threshold itself. Such a seizure is masked by the continued passage of the stimulating current and the resulting refractoriness is itself sufficient to leave a true increase of about 100 per cent in seizure threshold when tests are made at five-minute intervals. This explains the apparent increase in threshold found by other investigators who used prolonged stimulation and failed to record seizures unless they persisted beyond the stimulus period.

The above observations and analysis permit the conclusion that agents clinically effective against convulsive disorders need not be capable of elevating normal seizure threshold. It is widely accepted that clinical seizures are due to abnormally lowered thresholds, although such data as are available are not in agreement.^{10,19,23} In sharp contrast to the inability of diphenylhydantoin to elevate the normal seizure threshold is its ability to raise the experimentally lowered seizure threshold. On the basis of this and other evidence, it has been suggested by us that this particular drug is clinically effective either by raising abnormally lowered seizure thresholds or by preventing maximal interneuronal facilitation or both.^{16,43}

3. *Elevation of Electroshock Threshold Experimentally Lowered by Brain Cell Hydration.*

In the course of a study of the influence of brain electrolyte and water distribution on convulsive threshold, the technic of Darrow and Yannet was employed in rats to deplete extracellular electrolyte without loss of total body water. The resulting hydration of brain cells is accompanied by a considerable decrease in threshold for electroshock and metrazol seizures. It has been found that the above phenomenon provides a simple quantitative technic for the laboratory assay of potentially useful anti-convulsant drugs. The details of these experiments have been reported elsewhere.^{32,34,35}

Table II summarizes the ability of Tridione, phenobarbital and diphenylhydantoin to elevate the experimentally lowered electroshock threshold. Tridione and phenobarbital are approximately equally effective, whereas diphenylhydantoin is less so. Again it may be emphasized that although diphenylhydantoin is unable significantly to alter the normal electroshock threshold, it is capable of elevating the experimentally lowered threshold.

TABLE II
EFFECT OF TRIDIONE, PHENOBARBITAL AND DIPHENYLHYDANTOIN ON ELECTROSHOCK THRESHOLD LOWERED BY CELLULAR HYDRATION

Drug	No. of Rats	Dose* Mg./ Kg.	Electroshock Threshold† m.a. (Mean ± S.E.)			Per Cent In- crease in Hy- dration Thresh- old (Mean ± S.E.)
			Normal	4 Hr. after i.p. Glucose		
				Control	Drug	
Tridione.....	12	400	31 ± 1.4	13 ± 0.6	23 ± 1.5	79 ± 5.1
Phenobarbital.....	12	45	32 ± 1.0	14 ± 0.9	27 ± 1.3	92 ± 6.1
Diphenylhydantoin .	10	50	29 ± 0.9	13 ± 0.5	19 ± 0.9	47 ± 3.8

* Given i.p. except for diphenylhydantoin, s.c.
† 0.2 sec. stimulus duration.

4. *Modification of the Pattern of Maximal Electroshock Convulsions.* It has previously been reported by us^{40,42,43} that seizures produced in rats, rabbits and cats by electroshock intensities not far above thresh-

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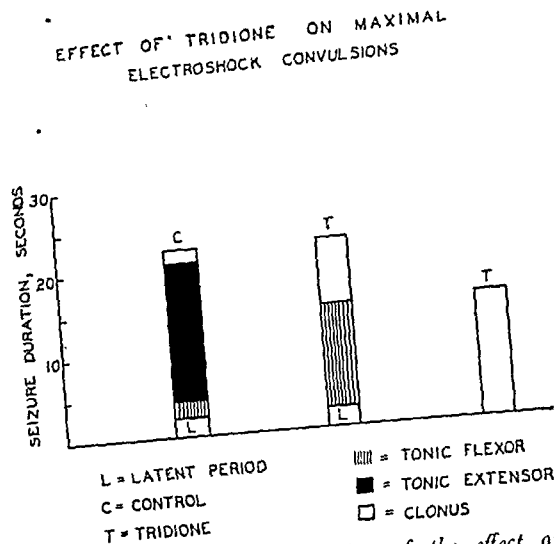


FIG. 1. Schematic representation of the effect of Tridione on maximal electroshock seizures in rabbits. Current intensity, 300 m.a.; stimulus duration, 0.2 sec. Protective doses (see text) of Tridione abolish the extensor component of the tonic phase (middle column). Larger doses abolish the entire tonic phase.

old are relatively constant in duration and are characterized by a relatively invariable motor pattern. In brief, the seizure pattern consists of an initial short tonic flexor component, a prolonged tonic extensor component, and a short terminal clonic phase, sometimes absent. Evidence has been adduced to indicate that the above described seizure pattern represents maximal inter-neuronal facilitation. The physiological properties of such maximal seizures and their modification by drugs have been described.^{17,33,43}

A number of anti-convulsant drugs are capable of altering the pattern of maximal seizures in experimental animals. A convenient end point for the comparison of anti-convulsant potencies has proved to be the abolition of the hindlimb tonic extensor component. By dividing the *minimal toxic dose* (that required to produce minimal signs of central impairment) by the *protective dose* (that required to abolish the hindlimb tonic extensor component), a *protective index* is obtained which makes possible a comparison of various drugs. To date, the drug ranking highest by this index is N-methyl-5,5-phenylethylhydantoin-

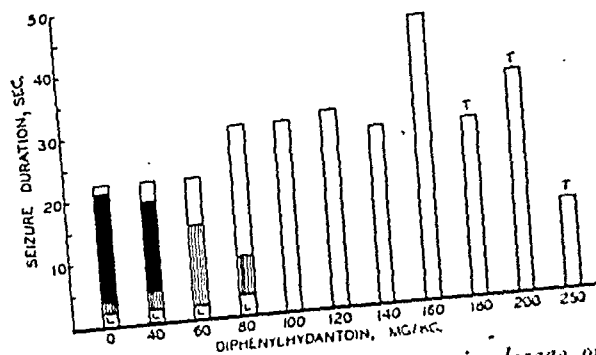


FIG. 2. The effect of diphenylhydantoin dosage on the pattern of maximal electroshock seizures in rabbits. Current intensity, 300 m.a.; stimulus duration, 0.2 sec. L=latent period. T=toxic dose. The barred, solid black and clear segments of the vertical columns represent tonic flexor component, tonic extensor component and clonic phase of the maximal convulsion, respectively. Observe the effect of increasing doses on seizure duration and pattern.

ate.^{*,33} Of the better known clinically employed agents, diphenylhydantoin, phenobarbital and Tridione rank in the order named.⁴³ Bromide is less effective and glutamic acid is completely without activity. It has been shown by us that glutamic acid exhibits no anti-convulsant potency by any laboratory procedure yet devised.¹⁷

TABLE III
RELATIVE ABILITY OF ANTI-CONVULSANT DRUGS TO MODIFY MAXIMAL ELECTROSHOCK SEIZURES IN RABBITS*

No. of Rabbits	Agent	Protective Dose Mg./Kg. (P)	Toxic Dose Mg./Kg. (T)	Protective Index (I = T/P)
10	Tridione	500	875	1.7
27	Phenobarbital	15	35	2.3
47	Diphenylhydantoin	60	180	3.0

* 300 m.a., 0.2 sec. (5 times threshold current).

P = dose required to abolish tonic extensor component of seizure in 50% of rabbits.

T = dose required to produce minimal signs of central impairment (ataxia, deficit in contact placing reaction, drowsiness, etc.).

Figures 1 and 2 illustrate the modification of the maximal seizure pattern by Tridione and diphenylhydantoin, respectively. The

* Kindly supplied by S. M. Fossel of the Sandoz Chemical Works, Inc.

TRIDIONE—METRAZOL ANTAGONISM
SPONTANEOUS EEG IN RABBITS

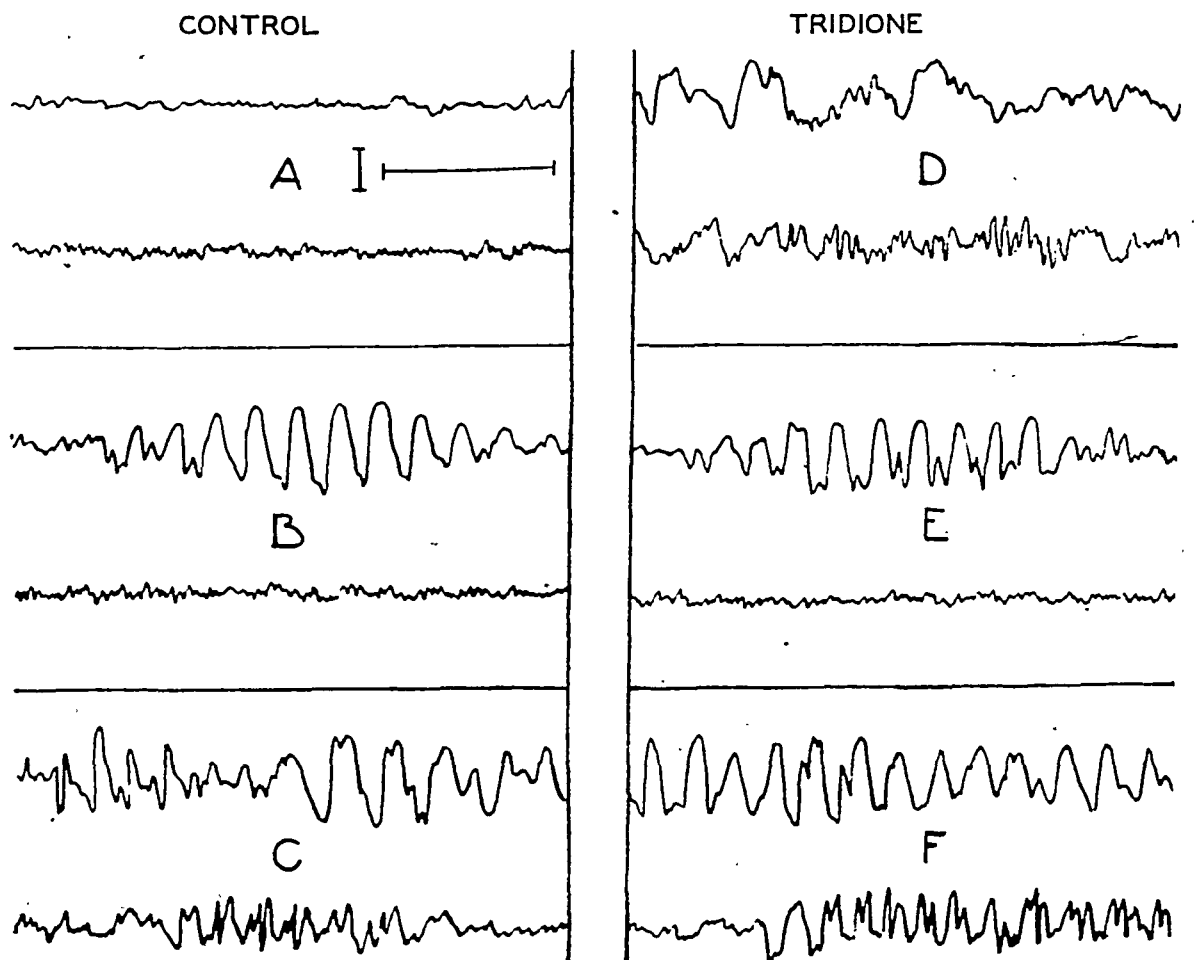


FIG. 3. Spontaneous EEG of the rabbit: Tridione-metrazol antagonism. A, B and C, control. D, E and F, after Tridione i.p., 700 mg./kg. Time and amplitude (as shown in A): horizontal line indicates one second; vertical line, 100 microvolts. EEG recorded from epidural electrodes, transoccipital (upper tracing in each pair) and transfrontal (lower).

A, control EEG without medication. Low voltage fast activity. B, episodic slow dysrhythmia in occipital lead after metrazol, 10 mg./kg. by slow i.v. infusion. C, almost continuous diffuse dysrhythmia after metrazol, 40 mg./kg., prior to overt seizure. D, irregular delta activity with spindles in motor lead ("sleep" EEG) after Tridione. E, occasional slow-wave episode after metrazol, 85 mg./kg. EEG otherwise normal. F, almost continuous diffuse dysrhythmia after metrazol, 110 mg./kg. This series illustrates the specificity of the Tridione-metrazol antagonism and the degree of protection afforded by Tridione against subconvulsive metrazol dysrhythmia.

comparative potencies of Tridione, diphenylhydantoin and phenobarbital in rabbits are given in Table III. Similar data have been obtained for rats and cats⁴³ and for man.³⁹

5. *Modification of Non-convulsive EEG Discharges Induced by Cortical Stimulation.* Various EEG effects of phenobarbital and other barbiturates have been described.^{1,4,6,9} and others. We have found that Tridione and phenobarbital do not significantly affect

the EEG in monkeys, rabbits and cats when given in doses less than those producing minimal signs of neurological depression. In larger doses, the typical EEG alteration is characterized by bursts of fast waves with intervening irregular slow wave activity typical of normal sleep. In contrast, diphenylhydantoin failed to cause EEG signs of sedation, even in toxic doses. The effect of Tridione on the human EEG is described later.

A more accurate analysis of cortical electrical activity has been made possible by recording the secondary cortical discharges following contralateral cortical stimulation with single condenser shocks. These discharges are closely related to the spontaneous electrical activity of the cortex at all stages of excitation and depression, but have the advantage of greater reproducibility.^{37,41} When doses were employed which produce neurological depression, the effect of Tridione and phenobarbital on the discharge pattern was essentially that described above for spontaneous EEG activity, namely, the production of a "sleep record." Smaller doses were without influence on the pattern of the evoked discharges. However, Tridione and phenobarbital in non-toxic doses moderately elevated the threshold for such evoked cortical discharges. In contrast, diphenylhydantoin even in toxic doses neither elevated threshold nor modified discharge pattern. Tridione and phenobarbital also prevented the typical modification in cortical discharge pattern produced by subconvulsant doses of metrazol. Tridione was twice as effective as phenobarbital in this respect, whereas diphenylhydantoin was inactive. The results are illustrated in Figure 3.

6. *Prevention of Metrazol-induced Petit Mal-like Cerebral Dysrhythmias.* Subconvulsant doses of metrazol given to rabbits subcutaneously or by slow intravenous infusion have been found by us to evoke spontaneous brief episodes of high amplitude, regular slow wave activity, with occasional alternating spike components but not accompanied by an overt seizure.³⁸ These discharges resemble in many respects the subclinical dysrhythmic episodes found in patients with petit mal. The dose of metrazol required for production of such discharges was found to be increased by Tridione (Fig. 4) and phenobarbital, but not by diphenylhydantoin. In equivalent

non-depressant doses, Tridione was approximately twice as effective as phenobarbital. Spike-dome dysrhythmia produced by fluoroacetate in dogs is also specifically prevented by Tridione.^{2,3}

II. CLINICAL STUDIES

Therapy of Convulsive Disorders. Eleven patients with slow wave EEG discharges and clinical seizures resembling petit mal were selected for Tridione therapy and study. The age and sex distribution of the patients, the various EEG types and the clinical results obtained with Tridione are shown in Table iv.

In all four patients with history of petit mal only and with a pure petit mal EEG (J. W., E. H., J. H., I. C.), complete clinical remissions were obtained. In two additional patients with petit mal EEG but with histories of both grand mal and petit mal (L. K., D. L.), both types of seizures disappeared under Tridione therapy. Complete remission was also obtained in one patient (W. S.) with atypical petit mal seizures accompanied by a clonic type of EEG discharge.

In the remaining four patients, all of whom had psychomotor as well as other EEG dysrhythmias, Tridione alone was inadequate to control seizures, although petit mal attacks were abolished in two (P. M., A. T.). At the present time one patient (R. C.) shows a substantially greater reduction in petit mal attacks under treatment with phenobarbital and diphenylhydantoin than with Tridione. Two individuals (A. T., A. A.) are completely controlled on Tridione and diphenylhydantoin. The remaining patient (P. M.) shows substantial improvement on Tridione and phenobarbital.

During complete clinical remission as a result of Tridione, the EEG was re-examined in four patients who originally had a pure petit mal type of dysrhythmia. Not

TRIDIONE — METRAZOL ANTAGONISM EVOKED EEG IN RABBITS

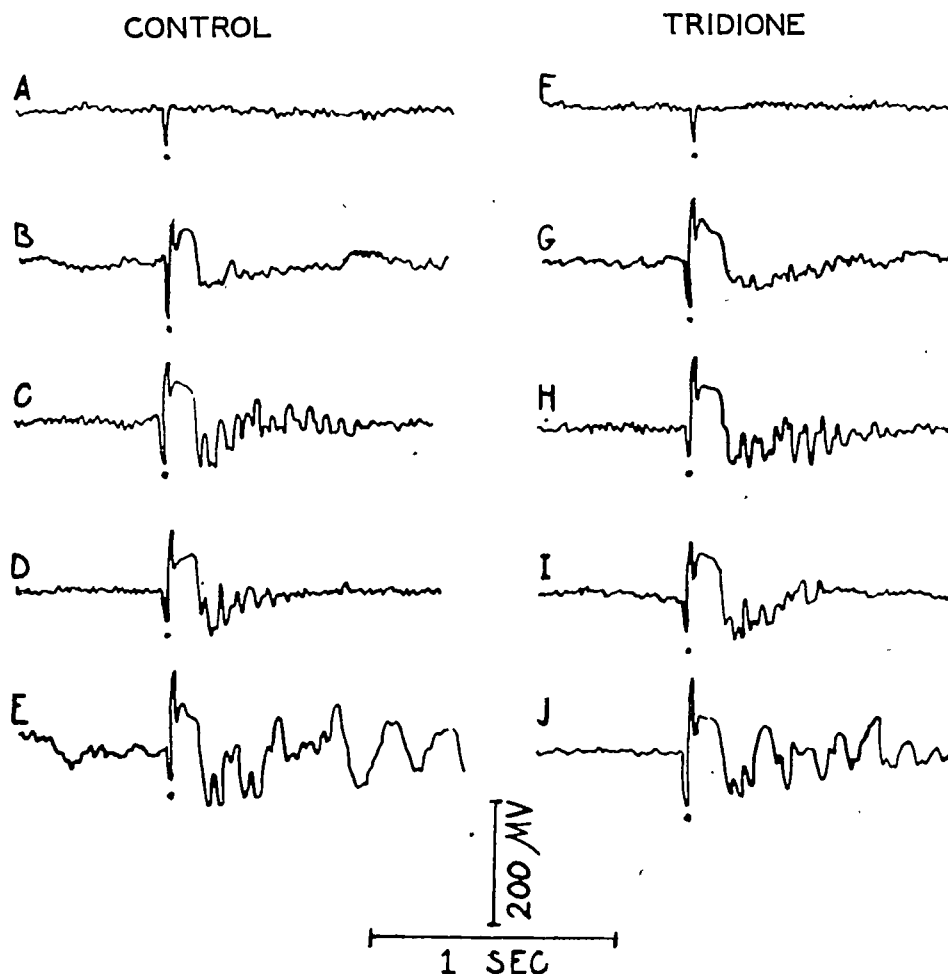


FIG. 4. EEG dischargee evoked by cortical stimulation in the rabbit: Tridione-metrazol antagonism. Dots indicate polarization artifact following condenser shocks (50 micro-seconds) applied to left hemisphere through epidural electrodes. EEG recorded from opposite hemisphere. Upward deflection indicates motor area electronegative to indifferent electrode. Time and amplitude as shown.

A-E, control. F-J, after Tridione i.p., 400 mg./kg. A and F, shock polarization artifact only (10 volts). B and G, surface-negative component of evoked discharge. Threshold 20 volts in control (B), 25 volts after Tridione (G). C and H, same as above plus long repetitive component elicited by increased voltage. "Light sleep" type of record, rare in control but predominant after Tridione. Threshold 30 volts in control (C), 40 volts after Tridione (H). D and I, briefer repetitive component characteristic of waking state, normally present in control (D); present after Tridione when 80 mg./kg. of metrazol had been administered subcutaneously (I). Threshold in both D and I, 30 volts. E and J, prolonged slow repetitive "metrazol" discharge following 40 mg./kg. of metrazol in control (E) and 130 mg./kg. of metrazol after Tridione (J). Threshold in both E and J, 15 volts. This series illustrates the quantitatively greater ability of Tridione to protect against metrazol than to elevate electrical thresholds.

only was the spontaneous EEG found to be normal, but it was now impossible to produce a petit mal discharge by means of the standard hyperventilation test. (Fig. 5.) Tridione failed to abolish the psychomotor type of dysrhythmia in three patients in

whom it was possible to re-examine the EEG, despite the complete or nearly complete clinical remission of all seizure types in two of these individuals. In patient A. A., the "petit mal variant" dysrhythmia (classified in Table IV as grand mal) was unaltered.

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TABLE IV
TRIDIONE THERAPY OF PETIT MAL

Patient, Age and Sex	Control Period					Tridione Therapy						
	EEG Type	Drug	Seizures per Week			Seizures per Week			Other Drug Added	EEG Type	Toxicity	Tridione Gm./Day
			PM	PS	GM	PM	PS	GM				
J. W. 9M.....	PM	P, D	45	0	0	0	0	0	..	N	Phot.	1.2
E. H.† 9F.....	PM	D	200	0	0	0	0	0	..	N	Sed.	0.6
J. H. 17F.....	PM	P, D, G	100	0	0	0	0	0	..	N	Phot.	0.9
I. C. 11M.....	PM	P	50	0	0	0	0	0	..	N	None	0.9
D. L.† 15M.....	PM	P, D	175	0	2	0	0	0	..	N	Phot.	1.2
L. K. 3M.....	PM	P, D	100	0	4	0	0	0	..	PS	None	0.3
W. S. 13M.....	PS, GM	None	†175	0	0	0	0	0	..	PS	Phot.	1.8
P. M. 17F.....	PM, PS	P, D	175	0	R	0	25	2	Rash	1.8
						4	0	0	P	1.2
A. T. 26F.....	PM, PS	P, D	100	0	1	0	0	3	..	PM, PS	None	1.5
						0	0	0	D	1.2
R. C. 18M.....	PM, PS	P, D	30	0	0	15	0	0	Phot.	2.1
						3	0	0	*D, P
A. A.† 27F.....	PS, GM	D	10	0	1	15	0	30	..	PS, GM	None	1.2
						0	0	0	D	0.6

P = Phenobarbital
D = Diphenylhydantoin
G = Glutamic acid
* = No Tridione

R = Rare
N = Normal
† Case histories given in the text
‡ = Tonic head component

PM = Petit mal
PS = Psychomotor
GM = Grand mal
Phot. = Photophobia
Sed. = Sedation

Tridione was withdrawn in four patients (J. W., E. H., D. L., W. S.) after complete clinical remission for at least two months. Seizures returned within one to sixteen days. Tridione therapy was resumed when the seizure rate reached fifteen per week, representing a period of one to five weeks without medication, and clinical remissions were again induced. Although we have not as yet observed the reported prolonged freedom from seizures following Tridione withdrawal,^{22,24} possibly because our patients had not been in clinical remission for a sufficiently long period of time, we have confirmed the observation that Tridione medication may be stopped abruptly without danger of a sudden return of frequent seizures or of "status epilepticus," differing in this important respect especially from phenobarbital.

In at least five patients the attack rate

was sharply increased the first day of Tridione therapy. (Figs. 6, 7, and 8.) In one patient (E. H.) who remained under close clinical and EEG observation during the hours immediately before and after initial Tridione administration, it is thought that the drug itself caused the temporary exacerbation of seizures, but the mechanism is not obvious. In two of the remaining four patients it is possible that the withdrawal of phenobarbital when Tridione therapy was started may have been a major cause of the increased seizure rate. It is also possible that the temporary exacerbation is more apparent than real. Inasmuch as both patients and parents, with understandable anxiety, are much more observant when any new therapy is instituted, mild seizures may have been recorded which ordinarily were overlooked during the control period. Perhaps the emotional stress of being

EEG BEFORE (A) AND AFTER (B) TRIDIONE

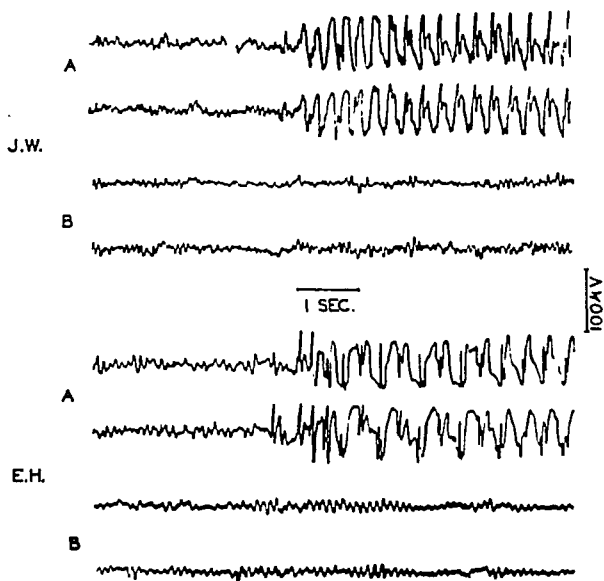


FIG. 5. Petit mal EEGs of two patients (J. W., E. H.) with histories of pykno-epilepsy. Time and amplitude as indicated. A—before, and B—after Tridione medication. Electrode placement: In each pair of tracings, the upper and lower leads are left occipital to parietal and right occipital to parietal, respectively. Before Tridione, both patients exhibited typical 3 per sec. spike-dome dysrhythmia early in the course of the standard hyperventilation test. During clinical remission there was a complete absence of petit mal dysrhythmia in both patients even after a double hyperventilation test.

under close observation was also a factor in the transient exacerbation of seizures.

Doses of Tridione varied from 0.3 Gm. per day to 2.1 Gm. per day. In general, age

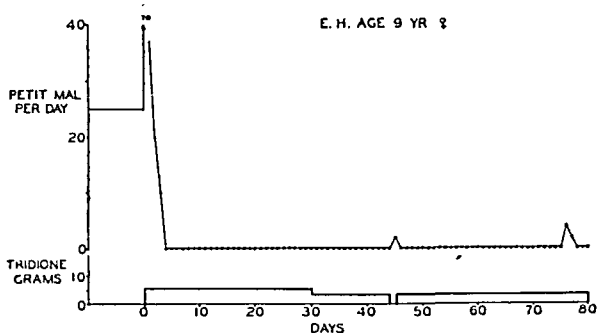


FIG. 6. Seizure rate before and after Tridione therapy in patient E. H. with a history of pykno-epilepsy and pure petit mal EEG. Details of the case are presented in the text and the EEG is shown in Figure 5. Note the increase in seizures during the first day of medication and the rapidity with which clinical remission ensued. A few mild seizures occurred during temporary omission of drug on the forty-fifth day and during an upper respiratory infection on the seventy-sixth day.

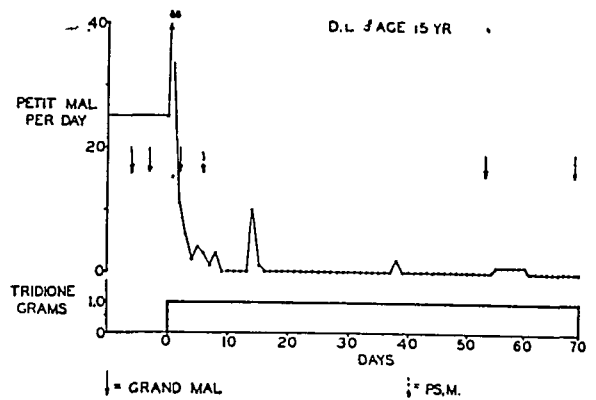


FIG. 7. Seizure rate before and after Tridione therapy in patient D. L. with a history of pykno-epilepsy associated with occasional grand mal attacks. Case details are presented in the text. Note the increase in petit mal seizures during first day of medication and adequate control of both types of seizures by Tridione alone. The exacerbation on the fourteenth day may have been due to paregoric; that on the thirty-eighth, to alcohol. The psychomotor attack on the sixty-ninth day was questionable.

and weight determined the initial dosage schedules but adjustments were frequently necessary on the basis of clinical response. In no instance were seizures brought under complete control in less than three days. Once the attacks had ceased entirely for several weeks, it was found possible in several cases to maintain complete remission on doses lower than those necessary for initial medication. (Figs. 6 and 8.) Oc-

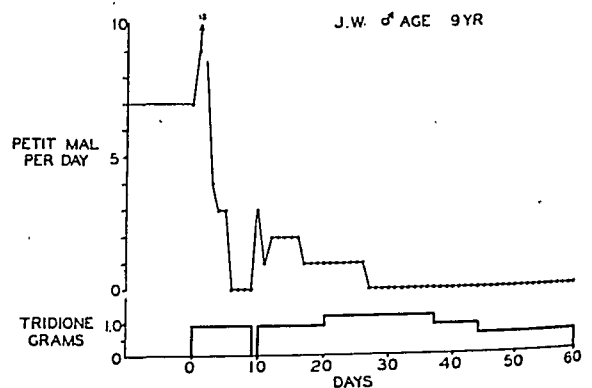


FIG. 8. Seizure before and after Tridione therapy in patient J. W. with a history of pykno-epilepsy for five years and with a pure petit mal EEG (see Figure 5). Note the increase in seizures during the first two days of Tridione medication, the inadequate control of attacks by insufficient dosage, the ultimate clinical remission and the final reduction in dosage without interruption of the remission.

casional escape from Tridione control of seizures was usually accountable for by intercurrent illness, unprescribed omission of the drug, etc.

Toxic side-effects from Tridione similar to those observed by others^{5,22,24,27} were frequent but not sufficiently troublesome to require interruption of treatment. Only four of the eleven patients reported complete freedom from side-actions. Five complained of photophobia and glare especially in bright light. Colored glasses frequently had to be worn. At the height of their photophobia, two patients noted transient inability to see objects distinctly. By adjustment of dosage, it was usually possible to decrease the visual disturbance without return of seizures. Sedation necessitated reduction in dosage in only two patients, but transient drowsiness was experienced by others, particularly early in the course of treatment. Should Tridione prove effective in petit mal only in doses producing sedation, the concomitant use of central stimulants (amphetamine, desoxyephedrine, etc.) may overcome the drowsiness without decreasing the anticonvulsant action.²⁷ The combined use of phenobarbital and amphetamine in grand mal lends precedent for this suggestion. A transient mild morbilliform rash with slight fever occurred in one patient, but disappeared promptly upon withholding Tridione and did not recur when the drug was cautiously resumed. One patient* not reported in this series experienced severe dermatitis, fever, headache, diarrhea, nausea and vomiting shortly after the initiation of Tridione therapy. The drug was immediately stopped and symptoms cleared, but reappeared upon resumption of Tridione. The petit mal was not improved and further therapy was not attempted.

The following brief case reports are

*We are indebted to Dr. S. S. Kauvar of Denver, Colorado for the clinical data on this patient.

illustrative of the use of Tridione in petit mal and in patients with mixed seizure types:

CASE REPORTS

CASE E. H. A nine-year old girl had pyknolepsy for one and one-half years unassociated with other seizure types. There was no relevant family history or record of illness or injury. Physical and laboratory examinations were entirely negative. Diphenylhydantoin therapy was ineffectual.

Seizure rate was 200 per week over a three months' control period of observation.

On three separate occasions, EEG examination showed diffuse symmetrical paroxysmal petit mal dysrhythmia occurring spontaneously and after brief hyperventilation. (Fig. 5.) EEG's of the father and three sisters were normal.

Tridione therapy was started at the dose level of 0.6 Gm. per day. An initial increase in number of attacks occurred during the first twenty-four hours but the seizure rate was reduced to zero by the fourth day of treatment. (Fig. 6.) In this patient it is believed that the temporary exacerbation of seizures was due to the drug itself. Complete clinical remission continued uninterrupted except for brief intervals (upper respiratory infection, temporary omission of medication, etc.). The EEG was re-examined during clinical remission and found to be normal (Fig. 5), even vigorous hyperventilation (two periods of hyperventilation lasting two minutes each with a minute of rest intervening) failing to elicit dysrhythmia. No side-effects were noted except mild sedation which disappeared upon adjustment of dosage. After absence of seizures for two months, Tridione was temporarily withheld. The EEG remained normal during the first week and freedom from clinical seizures persisted for ten days. Occasional mild attacks then occurred. Tridione was again administered three weeks after withdrawal and complete clinical remission quickly ensued.

CASE D. L. A fifteen-year old boy had pyknolepsy for four years with associated grand mal for seven months. The average petit mal attack rate was 175 per week; grand mal, two per week. Family history was negative except for migraine. Rapid skeletal growth and occipital

headaches were associated with the onset of grand mal but physical and laboratory examination were entirely negative. Phenobarbital and diphenylhydantoin, alone and combined, gave no relief from petit mal but may have reduced somewhat the grand mal attack rate.

EEG examination revealed diffuse symmetrical paroxysmal petit mal dysrhythmia occurring spontaneously and after brief hyperventilation. EEG's of the mother and sister were normal.

Tridione therapy was started at the dose level of 1.2 Gm. per day. An increase in seizure rate (from 25 to 85 per day) occurred during the first twenty-four hours, but the petit mal seizure rate was reduced to zero by the ninth day. (Fig. 7.) Complete clinical remission of petit mal continued without interruption except for three brief intervals, two of which were known to coincide with unprescribed ingestion of drugs (paregoric, alcohol). Grand mal was also considerably benefited by Tridione alone, the seizure rate being reduced from two per week to only one attack in a period of over six months. One questionable psychomotor seizure also occurred.

The EEG was re-examined during clinical remission and found to be normal, even after vigorous hyperventilation. No toxic side-effects were observed other than moderate photophobia, controlled when troublesome by wearing colored glasses.

After three months of Tridione therapy, the drug was withdrawn. Freedom from clinical seizures continued for sixteen days at which time occasional mild petit mal but not grand mal recurred. Tridione was again administered five weeks after withdrawal, and complete clinical remission was restored in one week.

CASE A. A. A twenty-seven-year old female had a long history of seizures dating back to the age of three when attacks diagnosed as petit mal were first observed. Falling seizures without convulsions started at the age of six. Grand mal appeared at the age of thirteen and a particularly severe and prolonged grand mal episode at this time was followed by left-sided hemiplegia which cleared slowly over a period of five months. The patient was periodically studied at several neurological clinics. Com-

plete roentgenographic examinations including pneumo-encephalograms were negative. EEG examination elsewhere disclosed focal right parietal dysrhythmia of an unstated type in addition to a diffuse dysrhythmia, also undescribed. Physical examination was negative except for some residual weakness and slight atrophy of the left extremities. A variety of medications had been employed. When first seen by us the patient was on diphenylhydantoin and a modified ketogenic diet. Seizures clinically resembling petit mal were occurring at the rate of ten per week. Grand mal attacks averaged one per week. The family history was negative.

Diphenylhydantoin was discontinued, and an EEG examination performed four days later revealed diffuse high amplitude slow wave dysrhythmia (5 per sec.) and paroxysmal focal dysrhythmia (2 per sec. spike and slow wave, "petit mal variant") in the right parietal region. Hyperventilation did not modify the EEG and did not elicit a typical petit mal dysrhythmia.

Tridione therapy was started at the dose level of 1.2 Gm. per day, and diphenylhydantoin was not resumed. The grand mal attack rate increased to five per day by the sixth day. The attacks were severe and followed by prolonged confusion and drowsiness. Petit mal was not significantly altered. Diphenylhydantoin was immediately resumed at the former dose level (0.3 Gm. per day) and the Tridione increased to 1.5 Gm. per day. Despite this regimen, drowsiness, disorientation, and agitated depression became so severe that the patient was hospitalized. The possibility of a toxic (drug) psychosis was entertained and Tridione was discontinued. EEG examination at this time was similar to that seen initially. However, slow but complete clearing of the psychosis concomitant with disappearance of grand mal over a period of two weeks and resumption of Tridione without untoward effect made the diagnosis of a toxic psychosis unlikely. It is believed that the acute psychotic episode was directly attributable to the withdrawal of diphenylhydantoin and the resulting marked exacerbation of the grand mal. After several adjustments of dosage schedule, the patient became free of all types of seizures on diphenyl-

hydantoin (0.2 Gm. per day) and Tridione (0.6 Gm. per day). No untoward reactions to Tridione were observed.

The experience in this case indicates the difficulties which may be encountered in a patient with mixed seizure types when medication for grand mal is suddenly replaced by Tridione alone.

COMMENTS

Until the introduction of Tridione there was no adequate therapy for petit mal. Phenobarbital and diphenylhydantoin afforded partial relief in a small number of cases and an occasional patient responded to amphetamine or caffeine. More frequently, medication with bromide, phenobarbital or diphenylhydantoin either afforded no relief or exacerbated the seizures. Other barbiturates and glutamic acid were likewise ineffective. Inasmuch as approximately 45 per cent of the nearly 800,000 epileptics in the United States have petit mal and approximately 8 per cent have petit mal unaccompanied by other forms of seizures,²⁰ the discovery of Tridione as a specific agent in the symptomatic treatment of the petit mal triad represents an important therapeutic advance.

The results of the laboratory investigations presented above indicate that Tridione has unique pharmacological properties as an anti-convulsant, especially when compared with diphenylhydantoin and phenobarbital. Tridione but not diphenylhydantoin specifically antagonizes the convulsant effects of metrazol, raises the threshold for petit mal-like slow wave EEG dysrhythmias induced by metrazol, elevates the threshold for evoked cortical discharges and raises the normal electroshock seizure threshold. Tridione is inferior to diphenylhydantoin in ability to alter the pattern of maximal electroshock convulsions, and superior to it in ability to elevate electroshock seizure threshold lowered by cellular hydration.

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Tridione is not significantly different from phenobarbital with regard to indices involving electrical seizure thresholds, but is approximately twice as effective with regard to antagonizing the convulsant and subconvulsant EEG effects of metrazol. It is inferior to phenobarbital in ability to alter the pattern of maximal electroshock convulsions.

Of all the indices examined, the antagonism to metrazol represents the most striking anticonvulsant property of Tridione. Perhaps the specificity of Tridione in the therapy of petit mal may be elucidated by a better understanding of the mechanism involved in the metrazol-Tridione antagonism. To this end, experiments are being conducted which include studies of the electrolyte and enzymatic effects of these two drugs. Finally, on the basis of the animal experiments, it is suggested that metrazol is the best antidotal therapy for Tridione overdose, the incidence of which may increase with the growing clinical use of Tridione.

In general, the clinical results obtained by us are in agreement with those reported by others. Particularly instructive is the finding that preliminary EEG examination provides a sounder basis than the clinical history of seizure type for deciding whether Tridione should be used, either alone or in combination with other drugs.

The exacerbation of petit mal seizures observed during the first twenty-four hours of Tridione therapy has not been reported previously to our knowledge. Possible explanations for this phenomenon have been presented.

A remarkable feature of Tridione therapy of petit mal, observed by others^{22, 24} and confirmed by us, is the fact that once complete clinical remission has been obtained, it is impossible to evoke a petit mal EEG discharge even by strenuous hyperventilation. (Fig. 5.) Freedom from petit mal

attacks may persist for days or weeks after cessation of Tridione medication,^{22,24} that is, for a period of time considerably beyond the chemical persistence of the drug in the body.²⁷ It is of interest to note that the salutary effect on the petit mal EEG has been observed within a few hours after intravenous Tridione administration.¹¹

Toxic effects from Tridione include drowsiness, confusion, and tremor; photophobia, disturbances in color vision, and scotomas; dermatitis; and, very rarely, blood dyscrasia.²⁷ Sedation and photophobia are the most common side-actions and ordinarily do not necessitate cessation of medication. Tridione should be withdrawn promptly upon the occurrence of dermatitis, scotomas, anemia or leucopenia.

In the light of our own clinical experience and that reported in the literature, tentative recommendations for therapy of petit mal may be made, as follows:

1. If a patient has a clinical history of petit mal only and also a pure petit mal EEG, Tridione alone constitutes the best possible therapy. Complete cessation of seizures may be anticipated. Transient exacerbation of seizures by Tridione during the first twenty-four hours is not a contraindication to its use.

2. If a patient has a clinical history of petit mal and petit mal EEG but also has occasional grand mal for which therapy is not being administered, Tridione alone may be adequate to control both the petit mal and grand mal.

3. If a patient has both a petit mal history and petit mal EEG and also has grand mal which is under therapeutic control, Tridione medication should be added for the purpose of controlling the petit mal. Grand mal medication, particularly phenobarbital, should not be withdrawn when Tridione is started. If such withdrawal is contemplated, it should not be attempted until the petit mal has been under control for several

months. Either diphenylhydantoin or phenobarbital may be prescribed for grand mal in conjunction with Tridione for petit mal, the evidence to date being insufficient to warrant a preference.

4. If a patient has both a petit mal history and petit mal EEG but in addition has a psychomotor EEG (high amplitude regular 4 to 6 per sec. discharge) and is not under medication, Tridione alone may decrease the seizure rate, but the result may not be as good as that obtained with a combination of Tridione and diphenylhydantoin. Cases reported in the literature^{5,24} would indicate that if a patient has both psychomotor seizures and a psychomotor EEG and is not adequately controlled by diphenylhydantoin, the addition of Tridione may bring about more satisfactory clinical remission. If the patient is not on therapy, Tridione may be employed alone, but diphenylhydantoin may have to be added subsequently. It has been our experience that clinical improvement may not be paralleled by improvement in the psychomotor EEG.

5. If a patient has a "petit mal variant" type of EEG, phenobarbital or diphenylhydantoin is probably superior to Tridione. Tridione may be added if there is clinical evidence of petit mal seizures.

6. Tridione is a new drug. Clinical experience with it is as yet limited. It is capable of causing toxic effects, some of which are serious. Therefore, Tridione should be employed only in cases exhibiting clear indications for its use. Patients receiving Tridione should be under close medical surveillance.

SUMMARY AND CONCLUSIONS

1. The anti-convulsant properties of Tridione have been compared in animals with those of diphenylhydantoin and phenobarbital by six different laboratory techniques. Of all the results obtained, the marked

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antagonism to metrazol is the property which most sharply distinguishes Tridione from both diphenylhydantoin and phenobarbital. Of particular significance in relation to the known specificity of Tridione against petit mal is its ability to abolish the petit mal-like EEG dysrhythmia produced in animals by metrazol.

2. On the basis of EEG and clinical study of a selected group of patients with slow wave dysrhythmias, specific recommendations have been advanced for the clinical use of Tridione alone or in combination with other drugs.

3. A sharp rise in seizure rate may be observed in petit mal patients during the first twenty-four hours of Tridione therapy. This transient exacerbation is not a contraindication to the drug, and may be followed by complete clinical remission.

4. It has been confirmed that even vigorous hyperventilation fails to evoke petit mal EEG dysrhythmias once complete freedom from seizures has been obtained. Restoration of the EEG to normal is added evidence for the specificity of Tridione in petit mal.

5. Although freedom from seizures may continue for days or weeks after discontinuation of Tridione, it is suggested that withdrawal should not be attempted until the patient has been seizure-free for many months. However, abrupt cessation of Tridione medication does not entail the danger of "status epilepticus."

6. Drug treatment for associated grand mal should not be stopped when Tridione therapy for petit mal is initiated.

7. If psychomotor EEG dysrhythmia is associated with a petit mal history, diphenylhydantoin combined with Tridione is probably the treatment of choice. An occasional patient may respond well to Tridione alone, even though the psychomotor EEG is not significantly altered.

8. Toxic side-effects to Tridione include sedation, visual sensitivity to bright light

and occasionally dermatitis. As a rule, untoward reactions are not troublesome to the point of necessitating cessation of medication. Yet the occurrence of photophobia is a definite disadvantage, and the search for effective drugs lacking this property should continue.

9. Preliminary EEG examination provides a sounder basis than clinical history of seizure type for deciding whether Tridione should be used, alone or in combination with other agents.

10. Tridione is a new drug and consequently several years may be required for a final estimate of its clinical status. Nevertheless, it is unexcelled to date as a specific symptomatic therapy for petit mal. Elucidation of its mechanism of action should provide insight into the pathological physiology of convulsive disorders of the petit mal type.

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Effects of Total Pancreatectomy in a Patient with Diabetes^{*}

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WE wish to report physiologic and metabolic observations on a completely pancreatectomized man.*

The patient, already diabetic enough to require considerable amounts of insulin, had a carcinoma of the pancreas and underwent resection of that organ, together with the entire duodenum, spleen and left adrenal, all but a fragment of the stomach and most of the omentum. He recovered sufficiently to be up and about his room, but died some fourteen weeks after operation with recurrence of the neoplasm. Autopsy failed to reveal any residual pancreatic tissue.

CASE REPORT

F. W., No. 328218, an unemployed white male, aged fifty-two, was first admitted to the Albert Merritt Billings Hospital February 24, 1944, with the chief complaint of diarrhea of two years' duration. The diagnosis of sprue had been made, but treatment directed against this disease had been relatively ineffective. Nine months before admission, with the onset of polyuria, thirst and voracious appetite, the blood sugar had been found to be elevated and the diagnosis of diabetes had been made, but the patient had refused to take insulin. He had lost approximately fifty pounds in the preceding two years. His father had had diabetes and his

* This case has been reported in preliminary form elsewhere.^{1,2} The surgical aspects have been described by Brunschwig, Ricketts, and Bigelow.³

mother and maternal grandfather had died of carcinoma.

On physical examination, the patient was emaciated: height 188.6 cm. (74 in.), weight 55.5 kg. (122 lb.). Temperature, pulse and respiration were normal. The skin and mucous membranes were dry. The tongue was coated, but showed no atrophy. The thyroid was palpable but not definitely enlarged. The heart and lungs appeared normal. The blood pressure was 114/70. A sharp liver edge was barely palpable. The spleen was not enlarged. No abdominal masses were felt, and rectal examination revealed nothing abnormal.

Laboratory findings were reported as follows: Hemoglobin 13 Gm. per 100 ml.; red blood cells 4,380,000 per cu. mm.; white blood cells 9,000; differential count normal. The urine contained 4 plus sugar and a trace of acetone but was otherwise normal. The fasting blood sugar was 363, cholesterol 147, total lipids 800, calcium 9.6 mg. per 100 ml.; carbon dioxide 30.5, chlorides 93.4 and sodium 133 mM. per liter. The plasma proteins were 6.05 Gm. per 100 ml. (albumin 3.69, globulin 2.36). The value for serum amylase was 68 units. The stools were liquid to mushy, had a cheesy odor, were acid to litmus and contained an excess of fat and undigested food particles. Cultures revealed *Micrococcus pilosis* but no other pathogens, and no ova or vegetative forms of *Entameba histolytica* were found. A histamine test of gastric secretion showed a maximum of 60 clinical units at fifty minutes. X-rays of the esophagus, stomach and

^{*} From the Departments of Medicine and Surgery and the Frank Billings Medical Clinic, School of Medicine, The University of Chicago.

duodenal bulb were normal. The basal metabolic rate was — 19 per cent.

Because of the patient's emaciation and voracious appetite, he was given a high-caloric diet which, during March, consisted of C 701, P 102 and F 99. With protamine zinc insulin, 35 units, and crystalline insulin, 10 units per day, the blood sugars varied from 102 fasting to 268 mg. per cent in the afternoon, and the twenty-four-hour excretion of glucose ranged from 8 to 15 Gm. Diarrhea continued and the feces contained an excess of fat and nitrogen. During the latter part of March, the patient developed marked pitting edema of the feet and ankles, for which no cause could be found except an increased capillary fragility as demonstrated by the tourniquet test.* For three weeks during April, the patient consumed a diet of C 900, P 225, F 100 (5,400 calories), requiring 60 units of protamine zinc and 40 units of crystalline insulin daily. He was still hungry. From May 3rd to 12th, the diet was C 398, P 200, F 12 (glucose equivalent 500 Gm.), the total insulin dose varied from 40 to 65 units per day and the blood sugars ranged from 87 fasting to 273 mg. per cent in the afternoon, with the excretion of 6 Gm. or less of sugar per twenty-four hours. There were occasional insulin reactions. Abdominal pain, chiefly hypogastric but sometimes epigastric, occurred from time to time and was occasionally severe. The diagnosis was thought to be chronic pancreatitis, producing diabetes and diarrhea. Carcinoma of the pancreas was considered, but was deemed unlikely in view of the two-year history and the remarkable gain in weight during treatment. The patient was discharged May 14th weighing 72.4 kg. (159 lb.), which represented a gain of 16.7 kg. (36.7 lb.) in eleven weeks.

During the summer, the patient was followed in the clinic. In July, he complained of severe pain in the right upper quadrant, lasting for three days with an exacerbation of diarrhea. In August he developed jaundice, clay-colored stools, dark urine and pruritus.

He was readmitted to the hospital August

* A similar edema was observed in another patient with well controlled diabetes and pancreatic steatorrhea when he was placed on a very high carbohydrate diet. The phenomenon may be related to a high glycogen content of the skin.

29th. The weight was 68.2 kg. (150 lb.). Physical examination revealed no new findings except the jaundice and a more easily palpable liver. There were no abdominal masses. On a diet of C 400, P 200, F 35, and with from 55 to 80 units of insulin per day, glycosuria was satisfactorily controlled. Laparotomy performed September 7th (A. B.) revealed a carcinoma of the pancreas with extensive infiltration of the neighboring organs and tissues. Total extirpation of the pancreas, duodenum, spleen and left adrenal, together with all but a fragment of the stomach and a large portion of the omentum, was performed. Examination of the pathologic specimen showed the midportion of the body and tail of the pancreas to be replaced by carcinoma which, on microscopic study, was found to be of the duct cell type. Many of the islets in the remainder of the pancreas showed changes consistent with ordinary diabetes mellitus (Dr. George Gomori). (Fig. 1.)

The postoperative course was remarkably uneventful, nutrition being maintained by parenteral glucose and Amigen,* and glycosuria being kept within reasonable limits (8 to 32 Gm. per day) with from 30 to 100 units of insulin per day. During this period and thereafter until shortly before death the patient received by parenteral injection 10 mg. of Synkavite† daily, and 2 cc. of Betaline‡ and 2 cc. of Cenolate§ every second day. Feeding by mouth was begun on the ninth day and was well tolerated. On September 22nd, fifteen days after operation, the patient was up in a chair. For three months after this date special studies, which will be described presently, were carried out. The diarrhea was definitely more severe than before operation and the patient lost weight to about 56 kg. (123 lb.) during the first five weeks. The weight was then maintained at this level until two weeks before death. When the diet was kept at C 400, P 100 and F 12 (glucose equivalent

* A 5% solution of a pancreatic hydrolysate of casein with 5 per cent dextrose (Mead Johnson).

† 2-methyl-1, 4 naphthohydroquinone diphosphoric ester tetra sodium salt; high vitamin K activity (Hoffmann-LaRoche).

‡ 2 cc. ampule contains 10 mg. thiamin chloride, 4 mg. riboflavin, 150 mg. nicotinamide, 5 mg. pantothenic acid, 10 mg. pyridoxine hydrochloride (Lilly).

§ 2 cc. ampule contains ascorbic acid, 0.100 Gm. as sodium salt (Abbott).

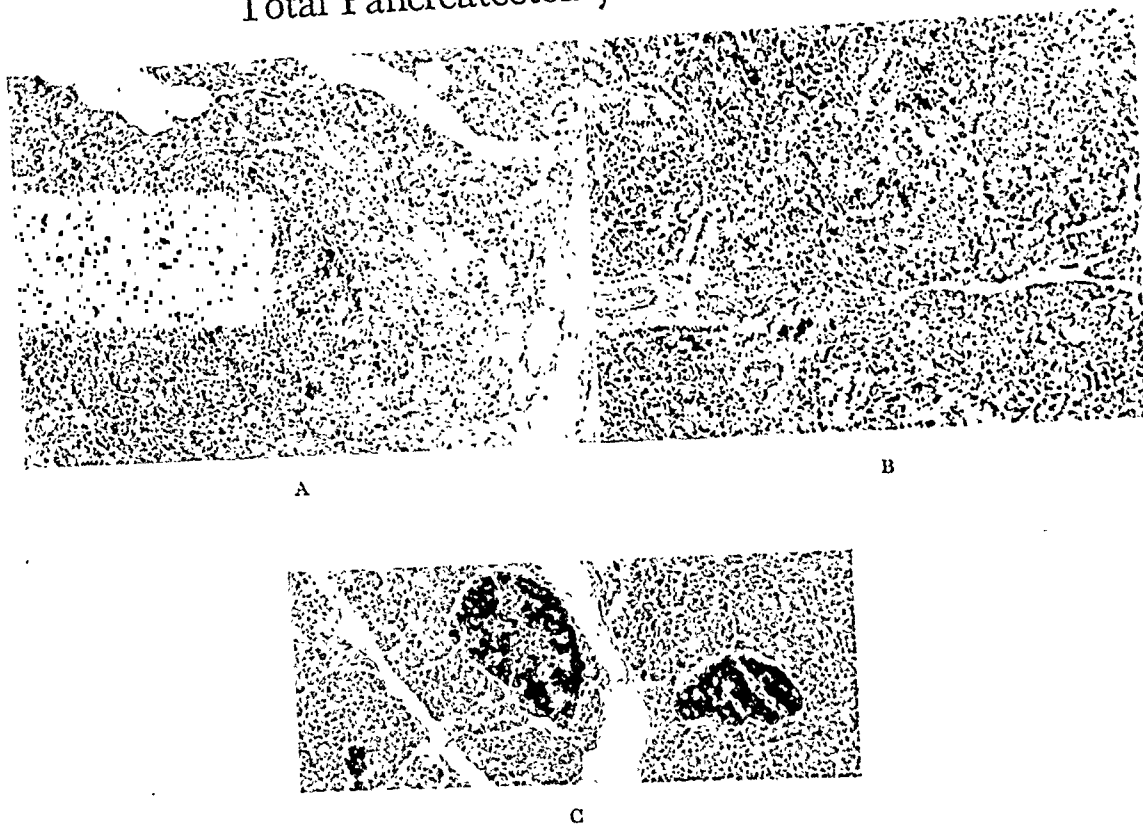


FIG. 1. A, a large island consisting almost exclusively of alpha cells and containing only a small number of beta cells (dark). Magnification $\times 115$. B, "ribbon type" islets. Magnification $\times 115$. C, normal islets from a non-diabetic patient, showing many beta cells (dark) Magnification $\times 115$. Description of the pathology of the islands of Langerhans (Dr. George Gomori): With ordinary stains the overwhelming majority of the islands look entirely normal except for an increase in size. An occasional islet shows hyalinosis. In addition there are a large number of "ribbon type" islets (W. G. MacCallum, *Am. J. M. Sc.*, 133: 432, 1907), many of which show thickened connective tissue stroma. Specific stains (G. Gomori, *Am. J. Path.*, 17: 395, 1941) show an extremely small number of beta cells, most of the islets being composed of over 90 per cent alpha cells. The granulation of the remaining beta cells seems to be normal. The alpha cells are large and richly granulated. In the "ribbon type" islets the cells are either agranular and unrecognizable as to type or contain a small number of normal appearing beta cells and very few alpha cells.

457 Gm.), glycosuria varied from 0 to 36 Gm. in twenty-four hours with a daily insulin dose of from 30 to 60 units, averaging about 40 units. By October 9th, jaundice was no longer visible and the liver was not palpable. On October 10th the Van den Bergh test of the serum showed 1.8 mg. per cent direct and 2.8 indirect of bilirubin with an icteric index of 19; a bromsulphalein test of liver function (dose, 5 mg./kg.) resulted in 36 per cent retention in 20 minutes. On October 24th, the values for the Van den Bergh test were 1.2 direct and 1.7 indirect, the icteric index being 11. On October 31st, with a dose of 2 mg./kg., there was 40 per cent retention of bromsulphalein in five minutes and no retention in thirty minutes. About October 17th, a tumor mass was palpable in the region of the incision. This grew steadily and about November 20th

abdominal pain recurred with increasing severity, requiring opiates. The patient developed anorexia and appeared to be going downhill rapidly. On December 4th all insulin was withdrawn for three days. On December 12th insulin was withheld permanently and the patient died December 18th in typical diabetic coma.

Autopsy was performed by Dr. S. D. Wu on December 18th, approximately five and one-half hours after death. An abstract of the pathologic report follows:

. . . The body is that of a markedly emaciated, icteric adult male, weighing 33.2 kg. (73 lb.) and measuring 167 cm. (67 in.) in length. The body is virtually skin over bones . . . The primary incision reveals practically no subcutaneous fat in the anterior abdominal wall. The peritoneal surfaces are thoroughly studded

everywhere with large numbers of grayish white and firm tumor nodules, averaging .5 cm. or so in diameter. These are more especially numerous in the anterior parietal peritoneum, the fascia and muscles to just beneath the skin. They are also numerous on the under surfaces of the diaphragm and in the omentum. Most of the stomach, all of the duodenum and the spleen are missing. . . . The heart weighs 280 Gm. and is normal in shape and size, only it is jaundiced. . . . The aorta and coronary arteries show the usual degree of atherosclerosis. . . . The liver weighs 1,520 Gm. and shows a number of small tumor nodules scattered about in the capsule. The organ is icteric. The gall-bladder is normal. The common bile duct is dilated, though not now obviously obstructed. . . . The pancreas as such is completely missing as far as can be judged by gross examination. In the region of the organ is a large and oblong piece of firm fibrous tissue with tumor imbedded in it. Serial sections of this reveal no grossly recognizable pancreas. . . . The remaining small segment of stomach, together with the lower end of the esophagus, is anastomosed to the upper jejunum. . . . In the middle jejunum there is a side to side entero-enterostomy. More distally in the jejunum the wall of the intestine is anastomosed to the much dilated common bile duct. All these anastomoses are healed, but bordered by neoplastic tissue. The duodenum is missing and there is a blind end at the site of the duodenojejunal junction. The intestinal serosa contains many tumor nodules throughout both the small and the large intestines. The right adrenal is normal. The left is not identified. Both kidneys together weigh 390 Gm. and are swollen and icteric.

The pertinent microscopic sections, reviewed by Dr. Eleanor Humphreys, are reported as follows:

Liver: The liver shows a fatty degeneration in the peripheries and even more in the centers of the lobules. The bile canaliculi are distended with bile while the interlobular connective tissue is the site of a pericholangitis. In most lobules this is an acute process with a predominance of polymorphonuclears but in some, lymphocytes and plasma cells are the outstanding type. The lumens of many of the larger bile ducts contain

bacteria, both rods and cocci, but at no place in the sections have these extended through the epithelium of the duct. There is an early, beginning cirrhosis with encroachment of the perilobular connective tissue upon the adjacent liver cords with resulting compression and degeneration. Many of the cords contain glycogen-rich hepatic cells. The cirrhou adenocarcinomatous tissue, composed, for the most part, of columnar epithelial cells lining alveolae or cystic spaces, can also be seen encroaching upon the liver (in the sections taken from the region of the hepatic vein).

Colon: Carcinoma cells can be found growing extensively under the muscularis. . . . A few tumor cells can be found growing in the lymph spaces between the circular and longitudinal muscular coats. . . . There is little inflammatory reaction. *Stomach and Jejunum:* The section passes through the site of the gastrojejunal anastomosis, now represented by a thin line of fibrous tissue. The carcinoma is penetrating through the muscularis into the submucosa of the jejunum and of the stomach. Below the muscularis the infiltrating fibroplastic tumor is forming large, irregular, neoplastic vesicles. . . . *Bile Duct and Jejunum:* . . . Neoplastic tissue has invaded the region of the anastomosis and infiltrates the wall of both jejunum and bile duct. . . . *Adrenal:* The orderly pattern of the cortex is disturbed by poorly demarcated nodules. Most of the cortical cells have eosinophilic granular cytoplasm, and the only cells with clear or foamy cytoplasm (suggesting an abundance of lipids) are found in small islands, near the capsule. Other acini of the glomerular zone are large and acidophilic with gland-like central cavitation. *Thyroid:* Fibrous bands subdivide the gland into nodules of varying size. The proportion of small (fetal type) acini is high, but all nodules contain normal colloid rich acini in considerable numbers. The epithelium is everywhere flat or low columnar. *Hypophysis:* The hypophysis has normal form and internal structure, but superficially, seems to have fewer basophilic cells than normal. Actually, the number is probably within the normal range. The chief abnormality is the comparative rarity of cells filled with deeply basophilic granules. In specially stained sections (Azur-carmin) many

Total Pancreatectomy—*Ricketts et al.*

lightly stained basophiles are observed. A small proportion, approximately 10 per cent, of the basophiles contain one or more vacuoles.

METHODS

The patient was confined to the metabolic unit of the hospital at all times and was weighed daily. All food and liquids were weighed or measured. As a rule, all stools were collected and weighed daily, and the twenty-four-hour specimens of urine were collected and preserved in a refrigerator for analysis. Samples of capillary blood for sugar determination were taken frequently, in the postoperative period usually four times daily. The technic of collection of specimens during the balance studies followed standard metabolic practice, aliquots of the food being saved and analyzed along with specimens of excretion.

Chemical determinations were made in duplicate according to the methods of the following authors: *in serum*, carbon dioxide content, Van Slyke and Neill,⁵⁵ pH, Hastings and Sendroy;²⁶ chloride, Wilson and Ball,⁵⁹ after digestion according to Van Slyke and Neill;⁵⁴ sodium, Butler and Tuthill¹¹ modified by Eichelberger;¹⁷ potassium, Shohl and Bennett⁴⁹ modified by Eichelberger;¹⁷ amylase by the saccharogenic method of Somogyi;⁵⁰ lipids, Wilson and Hanner⁶⁰ as modified by P. B. Donovan and described by Stewart et al.;³¹ calcium, Kramer and Tisdall³¹ modified by Clark and Collip;¹² phosphorus, Fiske and Subbarow;¹⁸ *in capillary blood*, glucose, Miller and Van Slyke;³⁹ *in plasma*, non-protein nitrogen, Koch and McMeekin²⁹ (protein was found by multiplying the difference between the total and the non-protein nitrogen by 6.25); total fecal fat, Saxon⁴⁸ modified by Fowweather.²⁰ Total nitrogen of food, feces, urine and plasma was determined by the Kjeldahl technic. Sufficient material to contain the appropriate amount of nitrogen was digested in 300 ml. digestion flasks with concentrated sulfuric acid and sodium and copper sulfates. The ammonia formed was distilled into 50 ml. of 4 per cent boric acid solution and titrated with 0.1 N acid to the bromcresol green end point as described by Meeker and Wagner.³⁸ Food, fecal and urinary calcium and food and

fecal phosphorus were determined by applying the methods used for serum to extracts or aliquots of the dried, ashed materials, made by several extractions with hot 10 per cent hydrochloric acid into volumetric flasks. After cooling they were made to volume and filtered through retentive paper. Dilutions were chosen so that 1 to 3 ml. contained 0.1 to 0.3 mg. of calcium. For calcium determinations such amounts were measured into the special centrifuge tubes, 1 ml. of 4 per cent ammonium oxalate was added, the mixture was roughly neutralized with concentrated ammonium hydroxide, and finally adjusted to pH 4.2 to 4.4 in the presence of bromcresol green. The determination was completed as with serum. For phosphorus, an amount of a dilution containing 0.3 to 1 mg. was used in the determination as described for urine.¹⁸ Inorganic phosphorus could be determined in urine by direct application of this technic.

The preparation and ashing of food and feces for analysis was done as described by Knowlton et al.³⁰

Respiratory studies were made with a Tissot apparatus (Dr. Irene Sandiford), gases being analyzed by the Haldane technic.

SPECIAL STUDIES

Effect of Diet and Medication on Fecal Volume. Before operation (Table 1) the average daily weight of feces without medication (March 28th to April 3rd and April 11th to 17th) was not significantly different from the weight when Lilly's enteric coated pancreatin tablets in doses of from 32 to 64 Gm. per day were being administered (April 4th to 8th). Reduction of dietary fat from 100 to 13 Gm. per day produced no important change in the amount of feces (March 28th to April 3rd and April 11th to 17th, as compared with April 18th to 25th); nor did any change result from the intramuscular administration of 3.5 ml. of crude liver extract per day. The fecal volume was appreciably reduced, however, in the period May 3rd to 11th when the carbohydrate of the diet was lowered from 901 to 398 Gm. and when tincture of belladonna, 30 drops, and bismuth subcarbonate, 6 Gm., were administered daily.

TABLE I

EFFECT OF DIET AND MEDICATION ON COMPOSITION OF FECES

Date	Diet			Medication	Stools					
	C	P	F		Average Weight		Total Fat		Total N (Gm./day)	
					Wet (Gm./day)	Dry (Per Cent of Wet Wt.)	Gm./day	Per Cent of Dry Wt.		
3-22-44 to 3-25, inclusive.....	701	102	99	None	934	11.2	20.4	19.5	6.45	
3-28-44 to 4-3, inclusive.....	900	225	100	None	1365					
4-4-44 to 4-8, inc.	900	225	100	Pancreatin, enteric coated, 32 to 64 Gm/ day	1488					
4-11-44 to 4-17, inclusive.....	900	225	100	None	1701					
4-18-44 to 4-25, inclusive.....	901	227	13	None	1350					
4-26-44 to 5-2, inclusive.....	901	227	13	Crude liver extract, i.m. 3.5 ml./day	1572					
5-3-44 to 5-11, inclusive	398	200	12	Tr. Belladonna, 30 drops/day. Bismuth subcarbonate, 6 Gm/ day	683					
9-7-44.....	Total pancreatectomy, gastrectomy, duodenectomy, splenectomy, left adrenalectomy									
10-20-44 to 10-25, inclusive	400	101	99	Atropine 0.0018 Gm. daily	2001	14	75.9*	26.6*		12.34*
10-26-44 to 10-29, inclusive	400	101	99	Atropine 0.0018. Pow- dered pancreatin 30 Gm. daily	1358					
10-31-44 to 11-7, inclusive	400	103	20	Atropine 0.0036. Pow- dered pancreatin 45 Gm. daily	750					
11-8-44.....	400	103	20	Powdered pancreatin 45 Gm. daily	5580					
11-9-44.....	419	103	20	Powdered pancreatin 45 Gm. daily	3360					
11-10-44.....	400	99	17	Atropine 0.0036 Gm. daily	60					
11-11-44 to 11-19, inclusive	400	103	20	Atropine 0.0036 Gm. daily	870					
11-20, 24, 25....	257	59	12	Atrop. 0.0036 Gm., Pancreatin 20-40 Gm.	672					
	295	74	14	daily						
11-21, 22; 23....	342	83	15	Pancreatin 40-60 Gm. daily	459					
	419	104	20							

* Two-day collection 10-24-44 to 10-25-44.

Total Pancreatectomy—Ricketts et al.

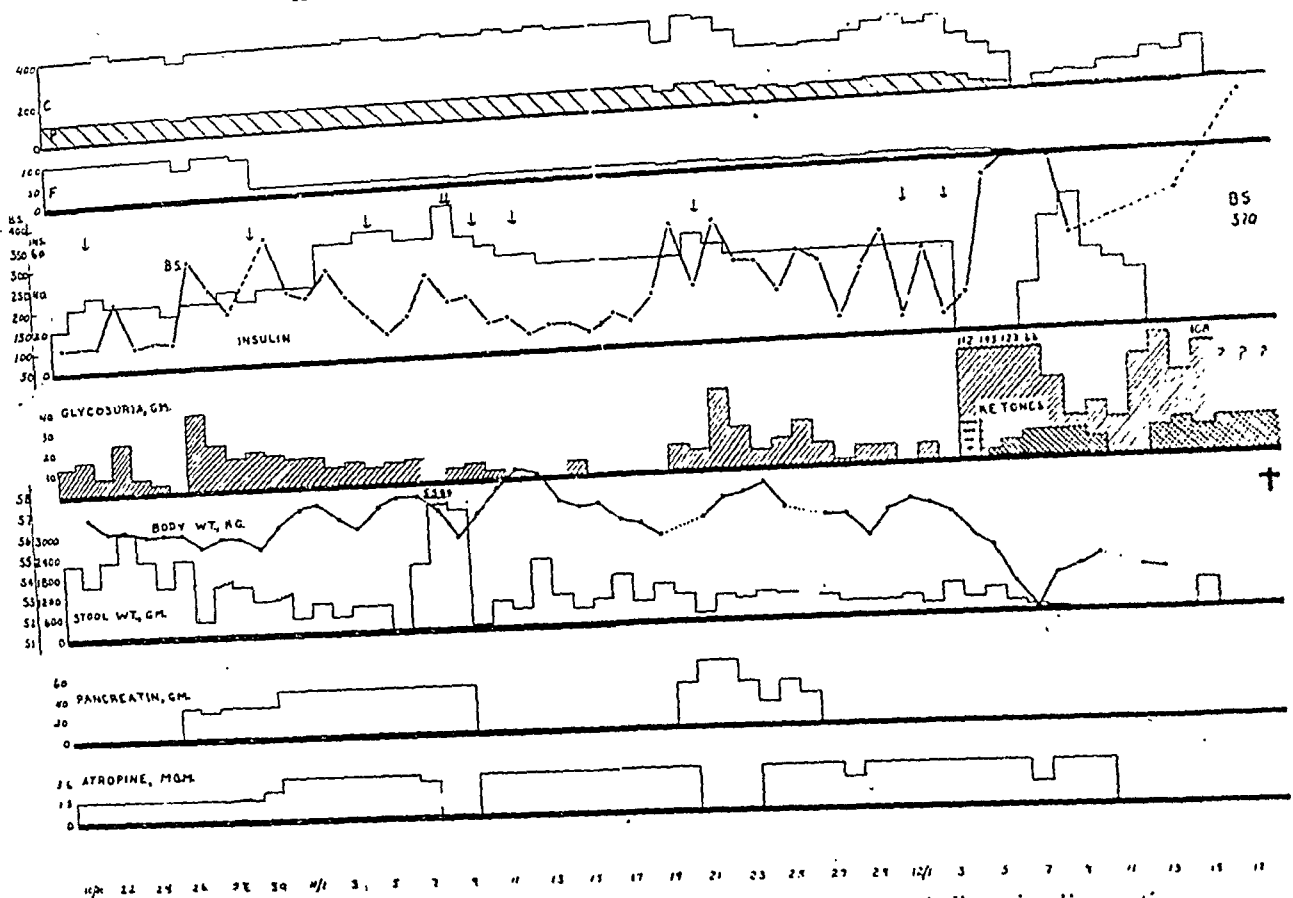


FIG. 2. Observations from six weeks after pancreatectomy until death; arrows indicate insulin reactions.

After operation the quantity of feces was so large as to render impractical the collection of specimens for chemical analysis in more than two-day amounts. Fecal weight during the period October 20th to 25th, when the patient

was receiving 0.0018 Gm. of atropine sulfate per day, averaged 2,001 Gm. daily. (Table I, Fig. 2.) The addition of 30 Gm. daily of pancreatin in powdered form (Lilly), now feasible because of the absence of gastric juice, was accompanied by a reduction in weight of stools to an average of 1,358 Gm. per day. This was further lowered to 750 Gm. per day when the dietary fat was reduced from 99 to 20 Gm., and when atropine was increased to 0.0036 Gm. and powdered pancreatin to 45 Gm. daily. When atropine was stopped November 8th, despite the continuation of pancreatin, the feces for that day weighed 5,580 Gm.; while in the period November 11th to 19th, with atropine reinstituted and pancreatin withheld, the average daily fecal weight was 870 Gm.

Absorption and Balance Studies. Before operation, no studies of carbohydrate absorption or of reducing substances in the feces were made. Nitrogen balances were not carried out since the urine was not analyzed, but the feces collected March 22nd to 25th contained an average of 6.45 Gm. of nitrogen per day. The patient's ability to absorb fat was not impaired as tested March 16th by following the serum lipids after

TABLE II
BALANCE STUDIES
Age..... 53
Weight..... 56.0 kg.
Height..... 188 cm.
Total pancreatectomy September 7, 1944
Diet: C 400, P 101, F 99, G = 471, Cal. = 2,895
Last feedings 7:00 p.m. each evening
Crystalline insulin 15-10-5 units
Fasting blood sugar October 24, 101 mg./100 ml.
Fasting blood sugar October 25, 111 mg./100 ml.

Date		Wt. or Vol. (Gm.)	N (Gm.)	Ca (Gm.)	P (Gm.)	Crea- tinine (Gm.)
10-24	Food	15.98	1.18	1.49	0.83
	Urine	395	2.52	0.12	0.28	
	Feces(4)*	2220(2615)†	12.34 av.	0.98 av.	0.98 av.	
	Balance	+1.12	+0.08	+0.23	
10-25	Food	15.98	1.18	1.49	1.19
	Urine	1075	4.68	0.14	0.59	
	Feces(3)*	1440(2515)†	12.34 av.	0.98 av.	0.98 av.	
	Balance	-1.04	+0.06	-0.08	
Mean	Food	15.98	1.18	1.49	
	Urine	3.60	0.13	0.44	
	Feces	12.34	0.98	0.98	
	Balance	+0.04	+0.07	+0.07	

* Number of stools per day.
† Figures in brackets indicate sum of urine and fecal volumes.

a fat meal. During the period March 22nd to 25th, however, with the dietary fat 99 Gm. per day, the patient lost in the stools an average of 20.4 Gm. of fat (19.5 per cent of the dry weight) daily.

After operation, two attempts were made to determine the absorption of carbohydrate by means of the usual tolerance tests. These were unsatisfactory, however, because in each instance the ingestion of the glucose solution was followed within a few minutes by a watery diarrhea. The feces on one occasion gave a 2 plus reduction with Benedict's solution. The blood sugar in one test rose to a maximum of 99 mg. per cent above the fasting level and in another the maximum increase was 81 mg. per cent. During the collection of October 24th to 25th, an average of 37 Gm. of "glucose" per day was found in the feces, as determined by analysis on the filtrate after deproteinization. The significance of this figure is doubtful, however, in view of the possibility that, on the one hand, some carbohydrate may have been destroyed by fermentation and, on the other hand, an indeterminate amount of non-specific reducing substance may have been present. Nitrogen balances, together with those for calcium and phosphorus, are shown in Tables II and III. With a daily intake of 15.98 Gm. nitrogen, the fecal loss averaged 12.34 Gm. (77 per cent of the amount ingested), or at least five times normal. This compares with 6.45 Gm. before operation. Figures for the urinary constituents for October 24th should probably be disregarded because of the possibility of incomplete collection as indicated by the low creatinine value for that day. Assuming the collection of October 25th to be complete, and of this we have no reasonable doubt, it is to be noted that the large loss of nitrogen in the feces was accompanied by the relatively low urinary nitrogen of 4.68 Gm. per day. The patient was thus in a negative nitrogen balance of 1.04 Gm. daily. For the same day the calcium balance was slightly positive and the phosphorus slightly negative. A fat tolerance test was not performed in the postoperative period. Absorption, however, was distinctly poorer than before operation, the feces on October 24th containing 75.9 Gm. of total lipids, or 77 per cent of the fat ingested.

Diabetes. All the observations to be described except where it is otherwise stated, were made after pancreatectomy.

Insulin Requirement: Comparisons of insulin requirement in the pre- and postoperative periods (Fig. 3) were made insofar as possible with conditions constant and in the absence of complicating factors. Before operation, on a diet of C 398, P 200, F 12 (glucose equivalent 511 Gm.), and with the body weight 72 kg., the requirement was from 40 to 65 units per day. From sixteen to twenty days postoperatively, on a diet of C 401, P 102, F 11 (glucose equivalent 459 Gm.) and with the body weight 60 kg., the dose was from 30 to 35 units per day. The apparent reduction in the demand for insulin may have been due first, to the lower glucose value of the postoperative diet, second, to the loss of 12 kg. of body weight and third, to the fact that the amount of insulin in the second observation was actually inadequate, hyperglycemia being present in the latter part of the day. From November 12th to November 19th (Fig. 2), with the patient on the same diet, but with the blood sugar better controlled and diarrhea minimal, the true requirement seemed to be in the neighborhood of 40 units per day.

Sensitivity to Insulin: The patient was relatively sensitive to insulin both before and after the pancreas was removed. Hypoglycemic reactions were common in both periods and their frequency and intensity were seemingly unaffected by the operation.

Diurnal Fluctuations of Blood Sugar: It has been observed by Möllerstrom⁴⁰ and others that the blood sugar in human diabetes undergoes spontaneous diurnal fluctuations relatively independent of food intake. These have been attributed to rhythmic variations in the function of the liver,^{1,19,27} but it has never been determined whether differences in insulin secretion by the pancreas might contribute to the phenomenon. Our patient, lacking a pancreas, presented an opportunity to test this possibility. While being maintained on 30 units of protamine zinc insulin per day which, as previously demonstrated furnishes a constant supply of insulin from the depots,^{37,44} he was fed uniform amounts of carbohydrate every two hours, and for three days the blood sugar was followed at

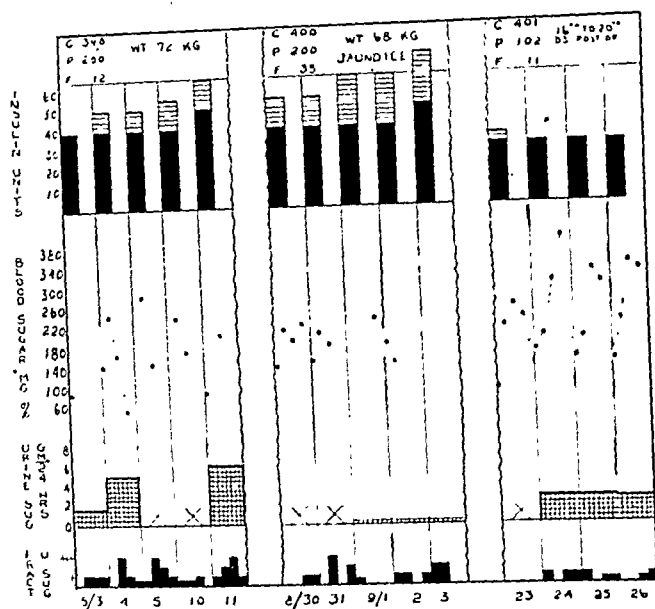


FIG. 3. Insulin requirement before and after total pancreatectomy; operation September 7th; protamine zinc insulin indicated by solid bars, crystalline insulin by cross-hatched bars.

two-hour intervals throughout each twenty-four hours. It is apparent from Figure 4 that with the supply of food and insulin at constant levels, the blood sugar showed a definite downward trend during the night.

TABLE III
COMPARISON BETWEEN ACTUAL AND CALCULATED FECAL NITROGEN (GM./24 HRS.)

	10/24	10/25	Mean
N intake.....	15.98	15.98	15.98
N in urine.....	2.52	4.68	3.60
N in feces (calculated)...	13.46	11.30	12.38
N in feces (actual)....	12.34 (av.)	12.34 (av.)	12.34

Fasting Blood Sugar with Regular Insulin: It is well known that severely diabetic patients maintained on crystalline insulin, the last daily dose being given before supper, commonly exhibit marked hyperglycemia the following morning. The patient in question did not behave in this fashion, as shown by the data for October 21st to 26th. (Fig. 2.) This was the only period in which the patient refrained from eating during the night and when no interfering studies were being carried out. Diet, insulin dosage and activity were constant and the diarrhea was relatively so. It will be noted that with the

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CONSECUTIVE 24-HR. BLOOD SUGAR CURVES
30 U. PZI EACH AM
44.3 GM. CHO EVERY 2 HRS.

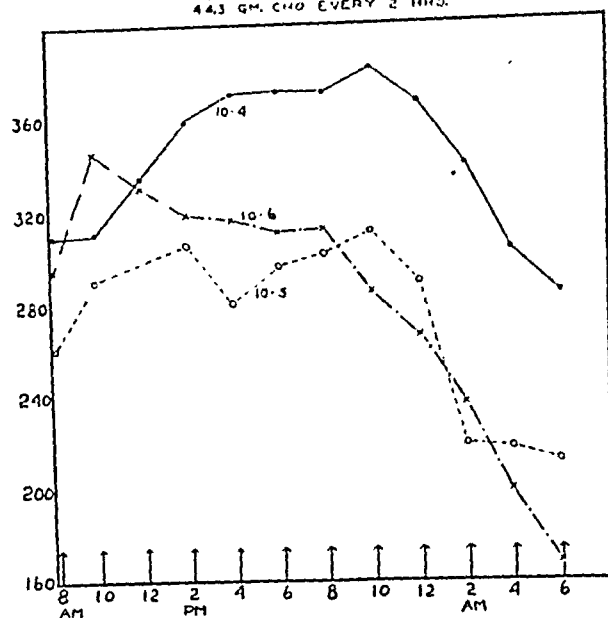


FIG. 4. Legend above illustration.

exception of October 23rd, when the patient had received orange juice during the night for an insulin reaction, the fasting blood sugar on each day did not exceed 111 mg. per 100 ml.

TABLE IV
BASAL METABOLIC RATES AND RESPIRATORY QUOTIENTS
Age..... 53
Height..... 188 cm.
Diet..... C 400, P 101, F 99
Insulin..... 10-5-5
15-10-10

Date 1944	Wt. (Kg.)	Total Cal./hr.	B.M.R.*	R.Q.	Non-Protein R.Q.
Oct. 21.	56.9	52.9	-18	0.77	
		53.2	-18	0.79	
Oct. 24.	56.0	53.8	-17	0.80	
		53.3	-17	0.79	
Oct. 25.	55.9	53.0	-18	0.77	
		52.6	-18	0.80	0.793
Oct. 26.	55.9	54.5	-15	0.79	
		56.2	-13	0.79	0.792

* Mayo Foundation Standards

Intravenous Glucose Tolerance Tests: Glucose tolerance could be measured only by the intravenous technic, since the oral method led to prompt and profuse watery diarrhea. Such a test, performed on October 26th after the patient had been receiving only crystalline insulin three times daily, gave a curve which, though

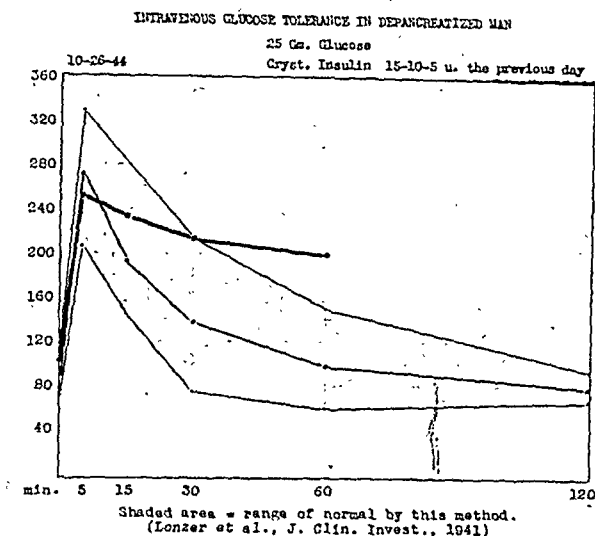


FIG. 5. Legend appears on illustration.

distinctly "diabetic," was less abnormal than in many cases of spontaneous diabetes. (Fig. 5.)

Respiratory Metabolism: Fasting total respiratory quotients were determined from October 21st to 26th, inclusive (Table IV), while the patient was taking a diet of C 400, P 101, and F 99 Gm. During this period the patient was given three daily doses of crystalline insulin, the last before supper. He received no protamine zinc insulin which, by its prolonged action, might have affected the fasting R.Q. The values obtained ranged from .77 to .80. An effort to measure the R.Q. after insulin had been completely withdrawn for several days was unsuccessful because of the patient's physical discomfort.

Non-protein R.Q. and the Metabolic Mixture: On October 25th, 4.68 Gm. of nitrogen were excreted in the urine. The following morning the non-protein R.Q. was .792. Calculations from these data and from the modified table of Zuntz and Schumburg, given by DuBois,¹⁶ indicate that on this day the patient was deriving 9.4 per cent of his calories from protein, 27.7 from carbohydrate, and 62.9 from fat.

The *D/N* ratio of the urine was determined on December 7th and December 17th to 18th. On the first occasion the last dose of insulin was given December 3rd. On December 6th the patient consumed carbohydrate 156, protein 33, and fat 6 Gm. (810 calories). He received no nourishment from 8:00 P.M. on December 6th until 10:00 P.M. December 7th. The urine collected between 6:00 A.M. and 10:00 P.M. on

December 7th contained 2.13 Gm. glucose and 0.88 Gm. nitrogen per 100 ml., representing a *D/N* ratio of 2.42.

On the second occasion the last dose of insulin was given December 12th. On December 16th the patient consumed only 6 Gm. carbohydrate (24 calories) and took no nourishment thereafter. The urine was collected by catheter from 11:00 A.M. December 17th, to 4:00 A.M. December 18th, when death occurred. This seventeen-hour specimen contained 4.20 Gm. glucose and 1.17 Gm. nitrogen per 100 ml., yielding a *D/N* ratio of 3.59.

TABLE V
SERUM AMYLASE

Date	Units
Mar. 21.....	68
Apr. 14.....	81
Sept. 7 Pancreatectomy	
Sept. 13.....	32
Sept. 14.....	9
Sept. 26.....	10
Oct. 17.....	66
Oct. 24.....	71
Dec. 5.....	35

Withdrawal of Insulin: On December 4th all insulin was withdrawn. On that day, the amount of sugar in the twenty-four-hour urine increased from less than 10 Gm. to 112 Gm., and on December 5th, 143 Gm. were excreted and the test for acetone was positive. The urine for December 6th or 7th contained 2.5 per cent glucose despite the fact that no food was eaten for twenty-four hours, and the test for diacetic acid became positive. On December 7th the serum carbon dioxide was 28 and chlorides 90.3 mM/L and the serum pH was 7.43. The patient had lost 4.6 kg. of body weight in three days and was very thirsty and uncomfortable. Insulin was then reinstituted with prompt relief of these symptoms. By December 12th the patient was in such suffering from recurrent carcinoma that it was decided to withdraw insulin as a terminal measure. The patient was now eating very little. Glycosuria again increased and ketosis this time appeared immediately, probably because of the preceding low intake of carbohydrate. On December 15th, 108 Gm. of glucose were lost in the urine and the patient became restless and irrational. Acetone and diacetic acid were now present in large amounts. On December 17th he was stuporous, the pulse

rose to 140 and respirations to 40 per minute; the blood sugar was 570 mg. per cent. Death occurred December 18th, after six days without insulin, in typical diabetic coma.

Miscellaneous Studies: Serum amylase (Table v), which was normal (68 to 81 units) before pancreatectomy, declined to 9 units one week afterward, but at the end of approximately six weeks had again returned to normal levels. These facts throw doubt on the hypothesis that the pancreas plays a major rôle in determining the amount of amylase in the blood and render uncertain the interpretation of such values.

There were no significant changes in values obtained throughout the patient's illness for serum CO₂, pH, Cl, Na, K, Ca, P or protein, except for a decline in Cl to 90.3 mM/L on December 7th after the first period of acidosis. No determinations of these substances were made after the final withdrawal of insulin.

COMMENTS

Certain features of this case require comment. The fecal volume after operation may have been influenced by factors other than the mere absence of the pancreas. For example, it was found at autopsy that the wall of the colon was diffusely infiltrated with carcinoma, which may have altered intestinal motility. At any rate, the amount of feces excreted daily was relatively enormous, ranging from 459 Gm. to 5,580 Gm. and averaging 1,500 Gm. to 1,800 Gm. Beazell, Schmidt, and Ivy⁴ in a study of four cases of pancreatic achylia, found the average daily fecal weight to be 441 Gm. and the highest 706 Gm. In the present case, fecal solids were determined in the postoperative period only once, when they amounted to 281 Gm., or approximately five times the normal.⁴¹ This compares with values of 80 to 120 Gm. found by Waugh et al.⁵⁶ in four cases of total pancreatectomy in man. In contrast to the experience of others,^{4,56} the administration of pancreatin in our case was not very effective in controlling diarrhea, atropine giving more satisfactory results.

The increase in the frequency and amount of the stools following pancreatectomy was reflected in a marked increase in fecal nitrogen and fat. It is of interest that with the large loss of 12.34 Gm. of nitrogen in the stools (77 per cent of the amount ingested) on October 25th, the urinary nitrogen, as if in compensation, was only 4.68 Gm. per day. Average normal values for fecal and urinary nitrogen are 1 to 3 Gm.^{4,15,32} and 10 to 15 Gm.,^{15,32} respectively, per day. Beazell, Schmidt, and Ivy in a summary of reported cases of pancreatic achylia state that an average of 61 per cent of the ingested nitrogen was excreted in the feces. In their own cases, this value varied from 40 to 100 per cent, one patient losing 13.3 Gm. of nitrogen daily in the stools. In the Mayo Clinic series of total pancreatectomies⁵⁶ fecal nitrogen ranged from 4 to 8 Gm. per day. Fecal lipids in our patient amounted to 75.9 Gm. during one twenty-four hour period, or 77 per cent of the fat ingested. The feces of normal persons contain approximately 10 to 15 Gm. of fat each day.^{4,52} In the literature dealing with pancreatic achylia, Beazell and his colleagues found an average of 62 per cent of the ingested fat excreted in the stools. In their own cases, with an intake of 112 Gm. of fat daily from 44.5 to 94 Gm. were lost in the feces, or an average of 66 per cent of the dietary fat. They state that absorption was materially improved by the administration of pancreatin. More closely akin to the present case are patients in whom the entrance of pancreatic juice into the intestine has been prevented by surgical operation, usually subtotal pancreatectomy. Whipple and Bauman,⁵⁷ in a study of three such patients maintained on a fat intake of from 75 to 100 Gm. per day, report that daily fecal fat varied from 3.2 to 81.2 Gm., representing excretion of from 3.2 to over 100 per cent of the ingested fat. The cases of total pancreatectomy reported by Waugh et al.⁵⁶

lost from 36 to 48 Gm. of lipids per day in the stools with an intake of 70 to 100 Gm. It is to be pointed out, however, that in many cases absence of the external pancreatic secretion is compatible with practically normal fat digestion and absorption.^{3,8,57}

It must be recognized that the diabetes in this case may have been influenced by certain factors which might render difficult a comparison with other forms of the disease. The absence of the pancreas undoubtedly impaired digestion and promoted diarrhea, thus tending to diminish hyperglycemia and insulin requirement. These tendencies were probably offset to some extent by the very high level of carbohydrate intake on which the patient was maintained. Furthermore, the direct entrance of food into the small intestine, owing to the absence of the stomach, may have resulted in an exaggerated response of the blood sugar to the ingestion of carbohydrate.²⁴ The possibility of adrenal cortical insufficiency due to the loss of the left adrenal would seem to be excluded by the patient's excellent postoperative recovery without replacement therapy and by normal values for serum electrolytes.

With due regard for these considerations, one may be permitted to comment on the fact that total pancreatectomy apparently failed to increase the severity of the pre-existing diabetes. This could be explained logically if it were assumed that the original disease had been associated with complete destruction or functional failure of the islet tissue. Histologically, while most of the islets in the portion of the pancreas not involved by carcinoma appeared normal with routine staining methods, specific stains showed a very small number of beta cells. It could not be stated, however, that either the number or the activity of these cells was so diminished as to spell "total diabetes" in the patient. Unfortunately, assays for insulin content were not performed on the extirpated gland. If, on the

other hand, some insulin were being produced before operation, it is difficult to understand the failure of the insulin requirement to rise afterward. Speculation might include the assumption of an extra-insular, "anti-insulin," factor which was removed by pancreatectomy. Of interest in this connection is the finding of Dragstedt¹³ that partially depancreatized dogs have a higher requirement for insulin than totally depancreatized dogs. Young,⁶¹ moreover, reports that when one of his dogs made permanently diabetic by injections of anterior pituitary extract was later depancreatized the insulin requirement was diminished. He states that this "may indicate that the acinar tissue of the pancreas plays a hitherto unsuspected rôle in carbohydrate metabolism." Similar results have been described by Thorogood and Zimmermann⁵³ utilizing dogs made diabetic with alloxan and subsequently depancreatized. The only evidence in man which points in this direction is the case described by Harvey²⁵ in which sub-total pancreatectomy in a previously non-diabetic patient resulted in diabetes necessitating 70 to 120 units of insulin per day. This is considerably in excess of the requirement of any human case of total pancreatectomy thus far recorded. In this institution the two patients who developed diabetes after subtotal removal of the gland exhibited only a very mild, and in one instance transient, form of the disease.¹⁰ One other patient with diabetes has undergone total extirpation of the pancreas.⁵⁶ It may be significant that that patient, who had been taking 20 units of insulin per day, was found after operation to need the same amount, namely 40 units daily, as did the patient in the present case.

The relatively low insulin requirement of approximately 40 units per day is in the same range as that found in other cases of total pancreatectomy. Eight such patients, in addition to the present one, have been

ported.^{23,35,46,56} Of these, three died within fifteen days of operation^{23,46} so that an estimate of their true requirement in the absence of complications could not be made. In one of the three patients,⁴⁶ moreover, a remnant of pancreatic tissue was found at autopsy. The daily dosages in these cases were from 26 to 50 units, approximately. Of the remaining five patients, one⁵⁶ died 2.5 months and another³⁵ nine months after operation; while three⁵⁶ had been living eight, fifteen, and thirty-seven months, respectively, at the time of reporting. The insulin requirement in these five patients ranged from 26 to 40 units daily. It thus appears that totally depancreatized men require no more than about 40 units of insulin per day. Does it follow that the output of insulin by the normal pancreas must be of this order of magnitude? Previous estimates of the secretion of insulin by the normal human pancreas have ranged as high as 200 to 300 units per day.⁴⁷ Holm,²⁸ however, calculated on the basis of experiments in depancreatized dogs that the adult human pancreas, if the caloric requirement were fully supplied by sugar alone, might secrete approximately 48 units per day—a figure in closer agreement with the findings in pancreatectomized patients. The observations of Dragstedt,¹³ Young⁶¹ and Thorogood and Zimmermann⁵³ referred to above are pertinent to the problem. The latter, in discussing their finding that alloxan treated dogs require more insulin before than after pancreatectomy, point out that since alloxan attacks the beta cells specifically, diabetes thus produced represents a pure (and presumably complete) insulin deficiency. The fact that the insulin requirement of these animals is much reduced by pancreatectomy suggests that this operation removes a substance either in the alpha cells⁵³ or in the acinar tissue which is antagonistic to insulin, and that the amount of the hormone produced by

the normal dog's pancreas can be estimated more truly from the requirement in alloxan diabetes than in the diabetes of complete pancreatectomy. To what degree this reasoning can be applied to man cannot be stated since strictly comparable experiments have not been carried out in that species. At any rate, the possibility must be recognized, on the basis of the observations on pancreatectomized patients, that in any case of diabetes requiring more than about 40 units daily, an *insulin antagonist* of some sort may be at work. "Insulin resistance," therefore, may begin at a much lower level of insulin requirement than heretofore believed.

The contour of the twenty-four hour glycemic curves confirms Möllerström's observations⁴⁰ concerning the diurnal fluctuation of the blood sugar in diabetic patients and demonstrates that this phenomenon can occur without variations in the supply of insulin and food. The findings do not constitute proof of his hypothesis, probable though it may be, that the liver is responsible for such fluctuations. The normal fasting blood sugars of October 21st to 26th while the patient was receiving crystalline insulin, and the relatively good tolerance for intravenous glucose are not characteristic of most diabetic patients who require 40 units of insulin per day. It cannot be stated on the basis of one case, however, that such behavior is typical of the depancreatized man, and its explanation in the present instance is not clear.

The respiratory quotients of .77 to .80 are definitely but not far below the generally accepted average of .84 for normal individuals. They are, however, considerably above the R.Q. of .70 exhibited by the totally depancreatized dog not receiving insulin.⁴³ Values for severe human diabetes obtained before the discovery of insulin are given by Benedict and Joslin⁵ as ranging from .69 to .77 with a mean of .74; by

Gephart, Aub, DuBois and Lusk²¹ from .66 to .97; and by Wilder, Boothby and Beeler⁵⁸ from .66 to .74. Most of these quotients approximate the R.Q. of pure fat oxidation. In our patient the total respiratory quotient would indicate that food-stuffs other than fat, presumably including carbohydrate, were being oxidized in the absence of endogenous insulin. Supporting this probability are calculations based on the non-protein R.Q. and the urinary nitrogen which show that on one occasion 9.4 per cent of the calories were being derived from protein, 27.7 per cent from carbohydrate and 62.9 per cent from fat. Comparable figures for normal individuals are indicated by DuBois, who states, "Under ordinary conditions . . . 10 to 20 per cent of the calories come from protein and 20 to 70 per cent from carbohydrate."¹⁶ By these standards, the number of calories furnished by both carbohydrate and protein in the present case was lower than the normal average but not below the normal minimum. It is fair to conclude that the oxidation of carbohydrate in the complete absence of the pancreas was by no means abolished fourteen hours after the injection of insulin.

The D/N ratios of 2.42 and 3.59 are of the same order of magnitude as those which have been repeatedly found for the depancreatized and the phloridzinized dog,⁴² respectively, and are in the same range as those reported by earlier authors in human diabetes.^{2, 21, 22, 34, 36} It is possible that the ratio of 2.42 obtained December 7th is too high because of the pouring out of glucose from the glycogen reserves of the days immediately preceding.⁶ The fact, however, that insulin had been withdrawn three days previously, with the consequent loss of from 112 to 143 Gm. of glucose per day in the urine, would suggest that the glycogen stores had undergone considerable depletion before the day in question. This criti-

cism is probably not applicable to the ratio of 3.59 obtained December 17th and 18th. On this occasion, insulin had been withdrawn four days previously and the intake of food had been practically zero (6 Gm. carbohydrate) on the day immediately preceding the observation. Cyril K. in the case described by Gephart, Aub, DuBois, and Lusk,²¹ showed ratios of 2.76 and 2.65 on two days of fasting which were preceded by two days of a practically carbohydrate-free diet, and in the case of William G., Allen and DuBois² found ratios from 2.28 to 3.82 when the patient was being fed almost nothing but protein. The depancreatized man then resembled severely and spontaneously diabetic patients and pancreatectomized and phloridzinized dogs in being able to convert roughly half his metabolic protein to carbohydrate.

Again reminiscent of the depancreatized dog are the promptness and extent of the ketosis, glycosuria, dehydration and loss of weight which followed the withdrawal of insulin. Many severely diabetic patients have themselves inadvertently proven that failure to take insulin may be fatal. An unusual combination of circumstances in the present case permitted the experimental verification, if indeed any were needed, of this fact. The patient's death in typical diabetic coma six days after the deliberate abandonment of treatment constitutes, so far as we are aware, the first instance in which the essentiality of a hormone for human existence has been demonstrated by the removal of the gland manufacturing that hormone and the subsequent withholding of replacement therapy.

The question of whether total pancreatectomy in man results in lipocytic deficiency cannot be answered by available data. The evidence of such deficiency in dogs, according to Dragstedt¹⁴ includes a fatty liver and a decline in both insulin requirement and serum lipids. In the patient under discussion

autopsy showed fatty degeneration of the liver, but this could have resulted from inanition and the terminal diabetic acidosis. Insulin requirement did not change appreciably. As shown in Table VI, the serum lipids, after the first postoperative month, fell from 20 to 30 per cent below the value found five days after operation, but never reached subnormal levels. The large amounts of pancreatin which the patient received for long periods of time may have served to prevent manifestations of lipocaic deficiency. It is of interest, however, that one of the patients reported by Waugh et al.⁵⁶ refused to take any lipotropic substances such as raw pancreas, lipocaic, lecithin and choline, yet suffered no decrease in serum lipids as late as thirty-seven months after operation and was feeling well and had no complaints.

SUMMARY

Pancreatectomy, the completeness of which was established at autopsy, was performed for carcinoma in a patient who was already diabetic and had chronic diarrhea. The stomach, duodenum, spleen, and left adrenal were also removed. For approximately three months the patient remained in sufficiently good condition to permit metabolic studies. Loss of the pancreas led to a marked increase in diarrhea, the daily fecal weight on one occasion being 5,580 Gm., even though the patient was receiving powdered pancreas in large amounts. Atropine was more effective than pancreatin in controlling fecal volume and its effect was augmented by a sharp reduction in dietary fat. Intestinal absorption of both fat and protein, already less than normal before operation, was strikingly diminished thereafter. The large loss of nitrogen in the feces (12.3 Gm. daily) was accompanied by the relatively low urinary loss of 4.68 Gm. per day. Analyses of food and excreta showed a slightly positive calcium and phosphorus balance, despite the severe diarrhea.

Extirpation of the pancreas was not followed by any increase in the requirement for insulin which, with a diet containing 400 Gm. carbohydrate, averaged about 40 units per day. Sensitivity to insulin was marked, the patient experiencing frequent hypoglycemic reactions. With the patient receiving constant feedings every two hours and a constant supply of insulin derived from the daily injection of protamine zinc insulin, the blood sugar exhibited a definite diurnal pattern, the lowest values occurring during the night. The phenomenon is presumably related to rhythmic variations in the activity of the liver. When the patient was maintained on three injections of crystalline insulin per day, the last dose being given before supper, the fasting blood sugars were essentially normal. This is contrary to the usual finding in severe, spontaneous diabetes. Also at variance with the behavior of such patients was the response in the present case to intravenously administered glucose, the resultant blood sugar curves being less "diabetic" than might be expected. The postabsorptive respiratory quotients varied from .77 to .80, values which are considerably higher than those for totally depancreatized dogs or severely diabetic human beings. Of the total calories derived from the metabolic mixture, 27.7 per cent came from carbohydrate, 9.4 per cent from protein and 62.9 per cent from fat. When insulin and food were withheld, the D/N ratio of the urine was 2.42 and 3.59 on two occasions, respectively. Permanent withdrawal of insulin resulted within six days in the death of the patient in diabetic coma. Values for serum amylase fell to low levels shortly after operation, but later returned to normal. One month after removal of the pancreas, serum lipids had declined from 20 to 30 per cent below the immediate postoperative value, but they never reached subnormal levels. Pancreatectomy produced no striking changes in serum carbon dioxide,

pH, Cl, Na, K, Ca, P, or in plasma proteins.

The considerable loss of nutriment through diarrhea may explain certain apparent differences between the diabetes in this case and the spontaneous disease of ordinary diabetic patients.

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Clearance of Inulin, Diodrast, Chloride and Phosphate under Mercurial Diuresis*

Intensive Study of a Patient in Severe Cardiac Failure

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THE purpose of this study was to trace as closely as our present technical facilities would permit, the course of a patient who was hospitalized in acute cardiac failure. The application of clearance tests, repeated at intervals of a week or two throughout his hospital stay of ten weeks, was chosen with the hope of obtaining information concerning the behavior of the functional renal components in extreme decompensation and under the influence of mercurial diuretics.

The use of inulin had manifest advantages, since its passage through the glomerular filter in the same concentration as in the circulating plasma, and its conduction through the tubules as an inert, non-metabolized substance, had been well established.^{1,2} The interval determination of its clearance value offered us, therefore, the filtration rate at moments during the clinical course of the patient when he was either suffering from marked fluid retention or was passing unusual volumes of urine. Furthermore, since the ratio of concentration of inulin in the circulating plasma and inulin in the urine could be influenced only by changes in the fluid volume by withdrawal of water by the lining cells of the proximal tubules, that fraction, or the U/P inulin, furnished us with an index to the amount of water reabsorbed and hence an insight into the function of the proximal segments. We were thus enabled to consider chloride

not simply in terms of urine concentration but in terms of water actually reabsorbed. The site of chloride resorption has also been located with some certainty in the distal tubules,^{3,4} and the ratio of urine chloride to serum chloride, considered in relation to the U/P inulin or the reabsorbed water, might be thought of as a function test of the distal tubules.

Diodrast was added to the infusion fluid because its mode of excretion by the cells of the tubules supplied useful information concerning the effective renal blood flow,¹ a factor which required investigation in a patient whose venous pressure was abnormally elevated.

CASE REPORT

The subject was a thirty-five-year old white male who entered Passavant Hospital on September 9, 1942, complaining of dyspnea, orthopnea, edema, marked gain in weight and pain in the legs. He had had "inflammatory rheumatism" in 1918 and had first given evidence of cardiac decompensation in 1938. From that time he had been in bed or inactive for long periods. Physical examination revealed a young man in acute distress, in whom edema was so extreme that the garments had to be cut from his lower extremities. A harsh systolic murmur was heard over apex and base, with pre-systolic and diastolic murmurs in the third and fourth left interspaces. The heart was markedly enlarged; coarse wet râles were heard in the bases and the liver was very large and tender.

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Mercurial Diuresis—Farnsworth

Edema was marked over the abdominal wall which also showed cyanosis below the level of the heart. The systolic blood pressure was 196, the diastolic 130. The erythrocyte count was 4,250,000, the hemoglobin 14.0 Grams. The leucocyte count was 7,150. Urine analysis showed albumin, two-plus, with scattered hyaline casts. The blood urea nitrogen was 19.0 mg. per cent, and the carbon dioxide combining power, 25.5 volumes per cent. The total protein was 6.65, with 3.92 Grams of albumin. The two-meter chest roentgenogram showed a mitral and an aortic configuration with a total cardiac enlargement of over 30 per cent. The electrocardiogram showed a right axis deviation with marked slurring of the QRS complexes and deformity of the T waves.

The acid-base balance was promptly adjusted, and the initial weight of 218 pounds was brought down to 197 by bed rest and diuretic management before clearance tests were performed.

The tests were done in the morning with the patient in the fasting state. The intake of fluids was at no time restricted, and the patient was encouraged to drink water according to thirst. Fluids were not forced in preparation for the tests. The usual technic for the inulin clearance was employed, the inulin and diodrast being added to sterile physiological saline solution. Catheters were introduced and the urine specimens were collected by rinsing the bladder with sterile water. The blood for the chloride determinations was taken under oil and estimations were done on serum and quoted in terms of sodium chloride. Three or four clearance periods were determined, the intervals ranging from fifteen to thirty minutes. The inulin, diodrast, chloride and phosphate were analyzed concomitantly, the method of Sendroy⁵ being employed for the chloride, that of Corcoran and Page⁶ for the inulin.

RESULTS

The results have been tabulated in Table I in which the volume of urine in cc. per minute, inulin clearance, diodrast clearance, chloride and phosphate clearance, U/P inulin, U/P chloride and U/P phosphate have been listed, with the dates upon which

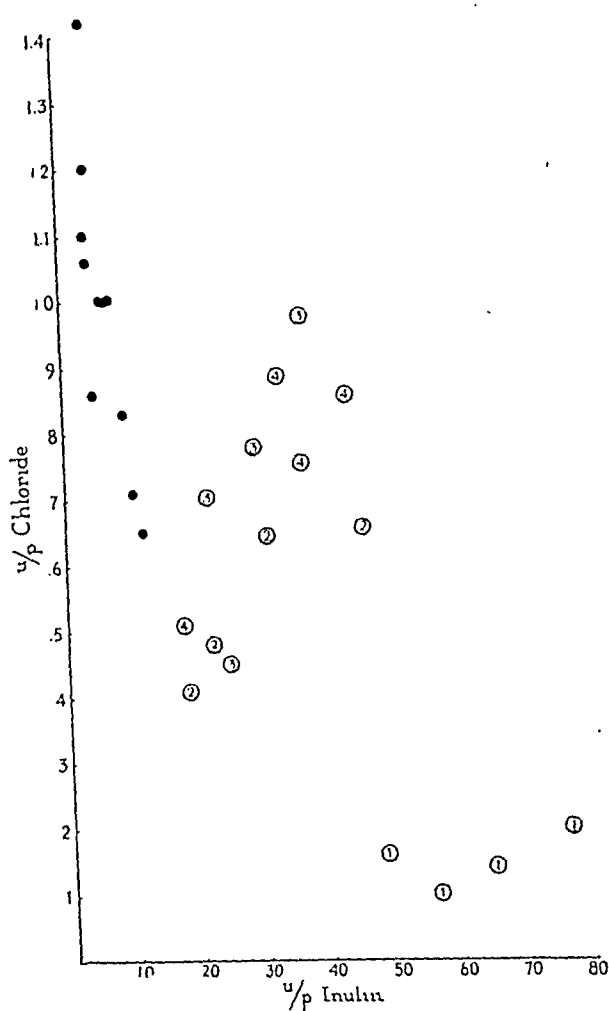


FIG. 1. Chloride excretion in patient with severe heart failure (A. Z.). Circles indicate clearance periods without mercurpurin. Dots indicate clearance periods in which mercurpurin was given prior to the test.

the tests were performed. Since the clinical improvement of the patient and the loss of the extreme edema which characterized his condition on admission introduced factors which required assessment, his weight on the morning of the test is also given.

The filtration rate as represented by the clearance of inulin was found to vary but slightly from test to test and the average clearance, three weeks after admission to the hospital, was almost identical with the final determinations just prior to discharge after the loss of fifty-two pounds of edema fluid. It was evident, furthermore, that diuresis with mercurpurin intravenously administered, failed to alter significantly the filtration rate, even with a urine volume of 19.8 cc. per minute.

TABLE I*

Mercupurin	Volume: Cc. per Min.	Inulin Clear- ance	Diodrast Clear- ance	Chloride Clear- ance	Phos. Clear- ance	U/P Inulin	U/P Chloride	U/P Phos.	Wgt.
<i>With Mercupurin</i>									
Oct. 16, 1942.....	6.6	69.1	157.5	4.68	22.0	10.5	.71	3.34	204
	7.0	65.4	147.8	5.89	24.7	9.3	.83	3.51	
	4.1	48.8	107.3	2.64	16.7	12.0	.65	3.79	
Nov. 10, 1942.....	19.8	77.0	177.5	14.20	31.9	4.7	.86	1.92	176
	13.4	83.0	154.0	13.70	26.8	6.2	1.02	1.99	
	8.4	66.0	121.8	8.60	21.3	7.8	1.02	2.54	
Nov. 16, 1942.....	10.9	75.4	141.4	10.70	23.9	6.9	1.00	2.20	173½
	10.5	50.6	147.8	15.60	35.6	4.8	1.43	3.40	
	11.8	51.7	140.9	14.50	30.5	4.3	1.21	2.56	
	15.5	61.8	179.2	17.20	36.8	4.0	1.11	2.41	
	17.3	69.4	199.1	18.40	37.1	4.0	1.06	2.16	
<i>Without Mercupurin</i>									
Oct. 8, 1942.....	.8	45.5	119.0	0.12	7.24	65.0	0.14	10.33	197
	1.2	57.7	135.0	0.19	10.34	48.5	0.16	8.60	
	.7	53.7	117.0	0.14	10.08	76.8	0.20	14.10	
Nov. 20, 1942.....	.5	30.8	55.3	0.09	3.98	56.8	0.10	7.05	169¾
	2.3	36.2	102.0	0.80	10.2	18.3	0.41	5.17	
	1.6	36.8	98.8	0.79	9.9	22.6	0.48	6.16	
Nov. 30, 1942.....	1.1	35.9	98.4	0.72	9.5	31.6	0.64	8.40	173¾
	1.1	59.8	157.6	0.71	10.0	46.7	0.65	9.18	
	2.2	54.0	121.6	0.96	12.3	25.2	0.45	5.74	
Dec. 11, 1942.....	1.5	55.7	131.9	1.44	13.7	37.4	0.97	9.21	165¾
	2.5	55.4	124.1	1.74	14.3	22.1	0.70	5.71	
	1.8	53.0	186.7	1.38	12.8	29.5	0.77	7.15	
	3.3	60.3	203.0	1.71	15.2	18.0	0.51	4.5	
	1.7	64.7	191.0	1.65	13.2	36.9	0.75	7.5	
	1.7	54.9	176.0	1.46	13.0	33.2	0.88	7.9	
	1.4	64.0	169.0	1.24	12.3	43.9	0.85	8.4	

* Data obtained from patient (A.Z.) in severe cardiac failure and under mercurial diuresis.

Somewhat more variation may be noted in the diodrast clearances; and the average of those periods completed on December 11th, when compensation had been more nearly restored, was higher than in previous tests. The individual periods also present fluctuations beyond what we have found under similarly controlled conditions in individuals with normal cardiovascular systems. Improvement in cardiac compensation, however, did not produce the consistent increase in diodrast clearance which improved circulation in the kidneys might have led one to anticipate. No correlation is traceable between the diodrast clearance and the large outputs resulting from mercurial diuresis.

With respect to the clearance of chloride,

at least two factors may be seen to have influenced the results, the most striking of which is the effect of mercury. The more copious the diuresis, the higher did the chloride clearance rise. This fact is in contrast with chloride clearances run in our laboratory on normal individuals with varying outputs, in which the clearance was found to vary only within a range of 0.5 to 3.0 cc. per minute, regardless of the urine volume. In order to analyze these figures in terms of tubular resorption, the U/P inulin was selected as an index to water reabsorbed and plotted against the U/P chloride. (Fig. 1.) This graph suggests the second factor which influenced the chloride data, namely, the progress of the patient toward compensation. In order to make this point clear, the

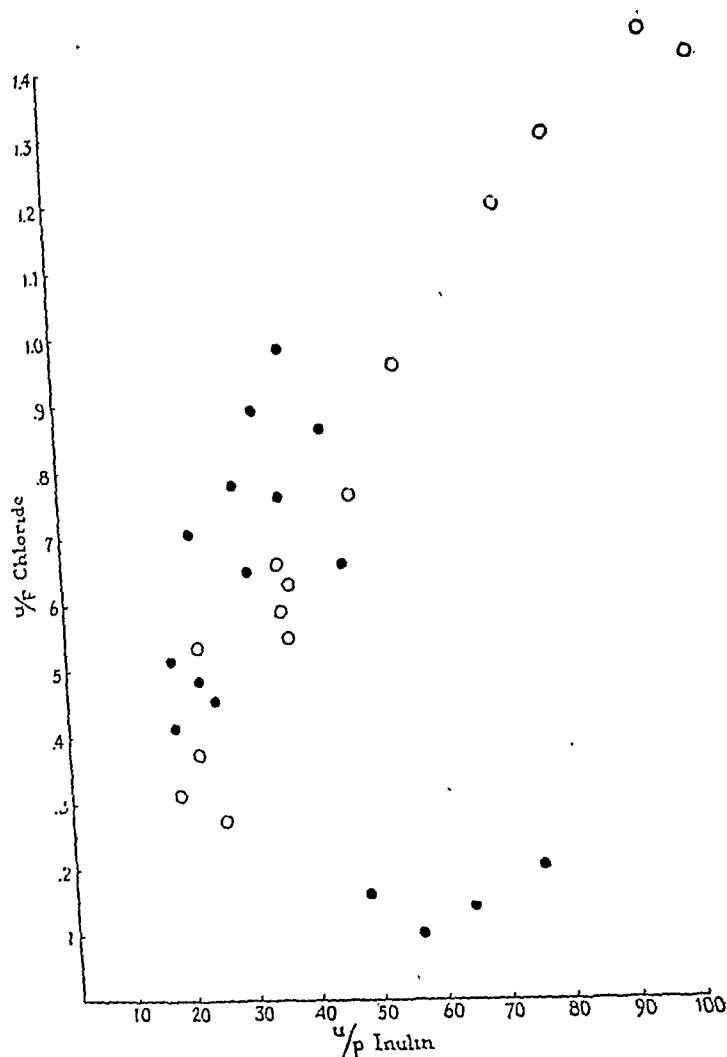


FIG. 2. Chloride excretion in patient with heart failure. Dots indicate clearance periods on A. Z. Circles indicate control series performed on normal subject, J. P. No mercurpurin was used in these determinations.

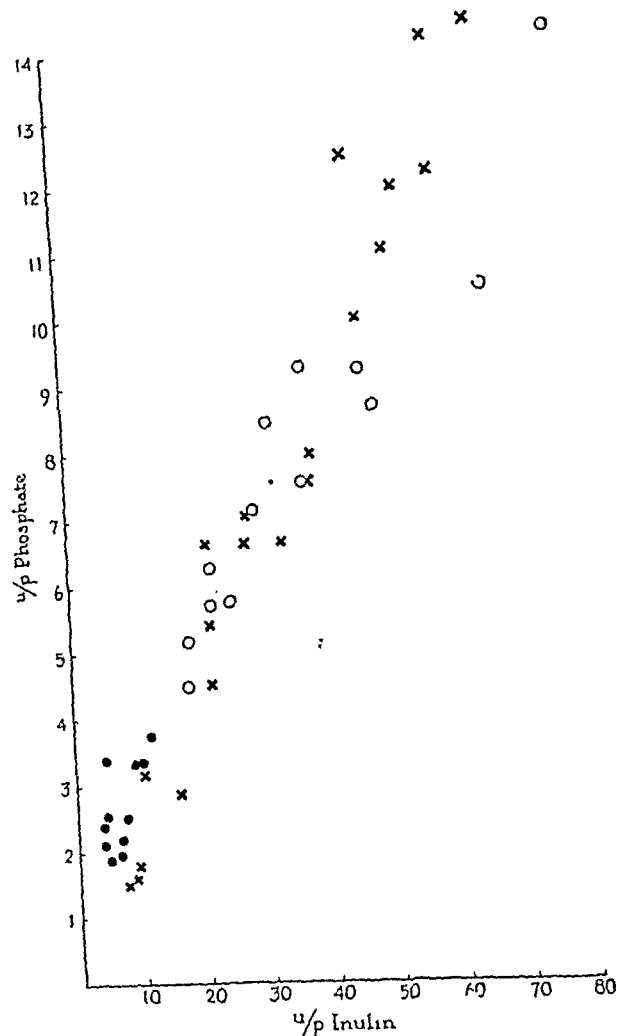


FIG. 3. Phosphate excretion in patient with heart failure. Circles represent A. Z., after administration of mercurpurin. Crosses indicate control series on subject, J. P.

periods completed on a given day have been marked by a number, the numbers being arranged to indicate a time sequence. The clearance periods performed without the use of mercurpurin show a wide scatter and have been plotted on a separate graph against those obtained from a normal subject (Fig. 2), in terms of U/P inulin and U/P chloride.

The phosphate clearance may be seen to bear a relationship to urine output, but a quantitative relationship does not appear to exist between phosphate and chloride. Plotting again in terms of U/P inulin, however, the results obtained under the influence of mercurial diuresis are found to follow pretty closely the curve described by periods in which mercurpurin was not employed.

This graph has in turn been combined with one taken from a normal individual without the administration of medical diuretics. Comparison of the regression lines shows the cardiac patient a little to the left, particularly in the mercurpurin periods of low U/P inulin ratio. (Fig. 3.)

COMMENT

The variable handling of water and response to diuretics characteristic of cardiac failure is a clinical commonplace. The present study, however, enabled us to ascertain that in this subject, at least, the variations in fluid and chloride balance did not occur as a result of changes in filtration rate or circulatory conditions, as reflected in the

diodrast clearance, throughout the period under investigation. The locus of action appears rather to lie in the proximal tubules. The filtrate has been formed as usual and at the same rate, regardless of the volume of urinary output. It could be proposed then, that the diminished output incident to the positive fluid balance of acute or chronic decompensation is a result of a specific change in reabsorption by the proximal tubules, similar to the influence of anti-diuretic hormone. If such may be accepted as a working hypothesis, the functional defect characteristic of heart failure would be thought of as an altered output of anti-diuretic hormone or as an altered threshold of renal tubular response to antidiuretic hormone in normal concentrations.

If we proceed to examine the fate of chloride in the distal tubules, the evidence is found to be inconclusive, since per unit of water reabsorbed in the proximal tubules, the U/P chloride shows no single trend. On October 8th the clearance periods yielded a high U/P inulin ratio but the chloride was far lower than normal. Later, however, although the U/P ratio of inulin and chloride still bore an irregular relationship to one another, they were roughly scattered about the regression line of the control studies and fell, if anything, somewhat to the left, thus indicating a tendency to increased U/P chloride at any given U/P inulin. The inconsistency of this patient's behavior toward chloride is difficult to account for, and further studies would be desirable on other decompensated patients. It may be pointed out only that the distal tubules appear to be specifically affected, and that the phosphate does not share the influence of the causes determining chloride disposal.

Turning now to the lower U/P inulin ratios, the effect of mercupurin on chloride is seen to be dramatic. In earlier papers^{7,8} we showed that in a normal subject, the

more closely the urine composition approximated the glomerular filtrate the lower the U/P chlorides, so that the projected regression line of U/P inulin against U/P chloride passed through zero. Such a figure could be regarded as a graphic presentation of the threshold theory. In our patient, on the contrary, the lower the U/P inulin, the higher the U/P chloride; the less the proximal tubules operate to withdraw water from the current of filtrate the less also do the distal tubules act to reclaim the chloride.

The failure of the diuretic to produce a similar effect on phosphate excretion suggests either that phosphate is handled by other tubular cells or that the effect is through a specific agency capable of affecting one out of several functions of identical cells.

CONCLUSIONS

1. Degrees of oliguria associated with cardiac decompensation were found to be unassociated with a decreased filtration rate or with a substantial or consistent decrease in effective renal blood flow.

2. Relations between the U/P ratio of inulin and that of chloride were variable, and did not describe the straight line which is characteristic of the normal subject. Such variations were found only to a slight degree in the case of phosphate.

3. The administration of mercupurin resulted in a large increase in U/P chloride at all U/P inulin ratios. This was not paralleled by a proportionate increase in U/P phosphate. It is, therefore, probable that mercupurin exercised a specific effect upon chloride disposal and that the site of such effect was the distal tubules.

4. The diuresis resulting from mercupurin was not correlated with an increased filtration rate, and circulatory conditions in the kidneys as indicated by the diodrast clearance were variable and described no definite trend. The site of action of mercu-

purin was, therefore, concluded to lie in the proximal tubules.

5. Comparison of U/P inulin and chloride ratios in this subject with those collected from normal subjects indicated that, while in the normal subjects water and chloride are dealt with in such fashion that the plotted data form a regression line passing through zero, under the present experimental conditions this physiological pattern breaks down and the graph suggests a simultaneous paralysis of both proximal and distal tubules with respect to water and chloride.

SUMMARY

A patient in severe cardiac decompensation was subjected to clearance tests of inulin, diodrast, chloride and phosphate over a period of eight weeks. The urinary output, daily weight and clearance figures, together with the U/P ratios of inulin, chloride and phosphate were tabulated. The U/P chloride was plotted against the U/P inulin in order to assess the reabsorption of chloride in the distal tubules in terms of water reabsorbed by the proximal tubules. The same was done in the case of phosphate.

Similar determinations were made under conditions resulting from the administration of mercupurin, and the data were plotted and compared with data drawn from experiences with normal individuals in varying degrees of water diuresis.

Evidence was found to support the idea that the oliguria of cardiac decompensation is not the function of a decreased filtration rate, and that the large outputs associated

with mercurial diuresis are not the results of an increase in filtration rate. It, therefore, appeared probable that the fluid retention of cardiac decompensation should be considered as referring directly to the renal tubules, and that the action of the mercurial diuretic was first on the proximal tubules and second and specifically upon the behavior of the distal tubules toward chloride.

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Chrysotherapy in Rheumatoid Arthritis*

A Three-year Study of 142 Cases

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THE use of gold compounds is now an established form of therapy for rheumatoid arthritis. Most men working in this field agree that a significant number of patients respond favorably to gold, that this number is greater and that the response of the individual patient is more favorable with chrysotherapy than with any other single form of treatment.¹ The prevalence of toxic reactions from gold has been a grave deterrent to its use. Thus far, reports on its efficacy have been concerned with the immediate response to therapy. It is the purpose of this paper to present the results of chrysotherapy in patients with rheumatoid arthritis from the vantage point of a three-year follow-up.

Material. These patients were studied and followed in the clinic and on the wards of the Presbyterian Hospital. The diagnosis of rheumatoid arthritis was based on the usual clinical and laboratory data, including x-ray, sedimentation rate and agglutination with group A hemolytic streptococci.² In all patients included, the diagnosis was concurred in by at least three internists. Extra care was used to exclude all cases of subacute rheumatic fever in which the prognosis is favorable without the use of chrysotherapy. The period covered in this report includes the years 1939, 1940, 1941 and half of 1942. The follow-up study was made in the fall of 1945 and thus the minimum period between gold administration and this follow-up is over three years. The group included only those patients who received

$\frac{1}{2}$ Gm. or more of gold compound, which has been considered to be an adequate amount. Patients who were unable to tolerate even this amount because of toxicity or who failed to continue treatment for any reason are not included. Using these criteria in that time, we treated 152 patients with rheumatoid arthritis with gold. We have adequate follow-up records on 142 of these patients. The ten on whom the data are inadequate had moved from the vicinity of the hospital and efforts to trace them have been unsuccessful. Thus this report is concerned with 142 patients with rheumatoid arthritis who have been treated with gold compounds and subsequently observed for at least three years. The group is, we believe, a representative one, comprising 74 per cent females. The age of onset of symptoms of arthritis ranged from sixteen to eighty years with a median of thirty-nine years. The median duration of symptoms before institution of chrysotherapy was four years. Thirty-seven per cent had a negative agglutination with group A hemolytic streptococci which is about average in a large group.

Immediate Response to Treatment. The immediate response to therapy is of a type which is generally accepted. We have divided the results into subjective response and objective response. In all but eight patients these two categories are in agreement. In these eight, the subjective response was marked, the objective only slight. Using the subjective response, 55 per cent showed

* From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York.

marked improvement, whereas using objective response 50 per cent showed marked improvement. Eleven per cent showed no improvement. In the remainder the improvement was definite but not startling.

Type of Gold. Three forms of gold compounds were used, myochrysin,* solganol B oleosum† and calcium aurothiomalate.‡ Seventy-two patients (50 per cent) received myochrysin, fifty-one (35 per cent) solganol, and nineteen (15 per cent) calcium aurothiomalate. Table I shows the results obtained with these three preparations. The differences are not statistically significant.

TABLE I
RELATION OF DRUGS USED TO THERAPEUTIC RESPONSE AND TOXICITY IN PATIENTS INCLUDED IN THIS SERIES, ALL OF WHOM WERE GIVEN AT LEAST $\frac{1}{2}$ GM. OF GOLD COMPOUND

Drug Used	No. of Patients	Not improved		Improved		Significant Toxicity*	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Myochrysin.....	72	4	5	68	95	28	39
Solganol B Oleosum...	51	8	15	43	85	16	31
Calcium aurothiomalate	19	2	10	17	90	4	21

* Significant toxicity is an arbitrary designation which includes all patients who developed a pruritis, rash, stomatitis, albuminuria or blood dyscrasia lasting more than one month.

Toxicity. Significant toxicity, that is a reaction such as dermatitis, or albuminuria of a duration of more than a month, followed the use of each drug. This is also shown in Table I and again the differences are not statistically significant. Of interest is the fact shown in Table II that significant toxic reactions following the use of gold compounds are related to the duration of the disease before the institution of such therapy. Reactions were more than twice as frequent in the patients who had had their disease over ten years as in those who had had the disease for less than one year. The dermatitides persisted for from one month to three years with a median dura-

tion of three months. Severe albuminuria lasted for one month to two years with a median duration of four months. Two deaths* occurred which could be attributed to the treatment, one due to aplastic anemia, the other to thrombocytopenic purpura. Two deaths occurred from other causes and could not be attributed to the use of gold, one following empyema of the gallbladder and the other a cerebral accident in an eighty-one-year old man.

Long-term Response to Treatment. The term "cure" has been used in describing the response of a patient with rheumatoid arthritis to gold. Viewed over a three- to four-year period, it becomes obvious that such a term seldom, if ever, should be used.

Eleven per cent of these patients showed no improvement with gold. Our experience would indicate that if a patient shows no response to 2,000 mg. of gold compound, further use of gold will bring about no improvement. Some of our patients have received 3 to 4 Gm. of gold compound with no improvement.

Thirteen per cent of the total group are still without symptoms of active rheumatoid arthritis from forty-five to seventy-eight months after the last injection of gold. However, 75 per cent did relapse. These relapses took place from one to fifty-eight months after the cessation of treatment. In general, the relapse was less severe than the original arthritis, but in all it was definite. The response to therapy with gold usually follows a clear-cut pattern and the relapse follows a similar pattern in reverse. Under treatment, the first symptom to subside is

* Gold has been used in this clinic for six years and we have treated 460 patients with gold compounds. These two deaths are the only ones we have had. The last received gold in 1942. Thus the treatment mortality in this group of 142 patients is misleading and corrected it should be 2 out of 460 or 0.4 per cent. The patient who died of aplastic anemia had several factors which might also have contributed, viz., carcinoma of the cervix which had been treated with radiotherapy, and syphilis treated with arsenic and bismuth. At the present time, we would not give such a patient gold therapy.

* Merck & Co.
† Schering Corp.
‡ Merck & Co.

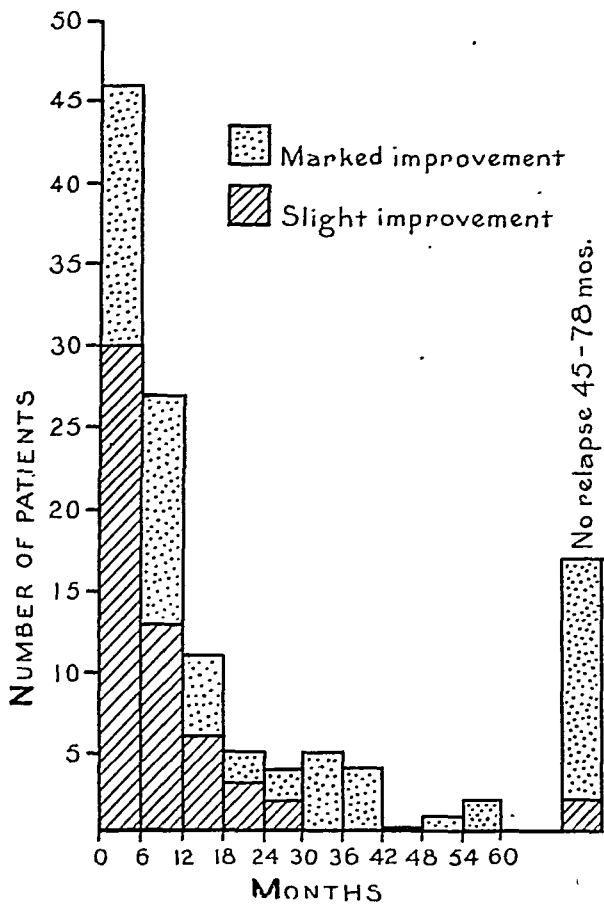


FIG. 1. The month during which relapse occurred following cessation of gold therapy. It is to be noted that there is a tendency for patients with marked improvement to relapse at a later date than those with slight improvement.

pain, the last stiffness. During a relapse, the first to reappear is stiffness to be followed later by pain. Swelling, redness and heat are variable. Generally, the sedimentation rate, if elevated, falls slowly but in a relapse the sedimentation rate may rise quite precipitously. The relapse rate bears no relation to the duration of the disease prior to therapy. Table II shows the percentage of

TABLE II
RELATION OF DURATION OF DISEASE TO THE DEVELOPMENT OF (1) TOXICITY, (2) THE RELAPSE RATE

	Duration of Disease Before Institution of Gold					
	Less than 1 Yr.	1-2 Yr.	3-4 Yr.	5-9 Yr.	More than 10 Yr.	Total
No. of patients.....	21	45	34	21	21	142
Per cent in whom significant toxicity developed.....	19	29	38	39	48	33
Per cent who relapsed..	76	73	70	76	72	75

relapses in the various groups in relation to the duration of the disease. The time of relapse bears a closer relationship to the type of improvement achieved on the first trial with gold compounds. Thus of the fifty-four patients showing slight objective improvement, a relapse occurred in one to thirty months, with a median of five months. In the group of fifty patients showing marked improvement (really arrest), a relapse occurred in one to fifty-eight months, with a median of eleven months. Two patients showing slight improvement and sixteen showing marked improvement have not relapsed at this writing. This is shown graphically in Figure 1.

Factors which account for relapse are not clear. The eighteen patients who have not relapsed at this time have been followed from forty-five to seventy-eight months. Only nine of these have been followed sixty months or more and we have three patients who had definite relapses in their fifth year after treatment had ended. Thus only nine patients of the group or 6 per cent could be classified as five-year cures. This number is too few to be considered significant. In general, one should expect relapse in a patient with rheumatoid arthritis who has had a remission with gold.

It is a fair generalization to state that the relapse is not as severe as the original disease. It is of great importance to realize that the patient who relapses has an excellent chance of improving again on chrysotherapy. This is shown in Table III. Because

TABLE III RESULTS WITH SUBSEQUENT USE OF GOLD			
Type of Improvement on First Course	Not Improved Again (Per Cent)	Improved Again (Per Cent)	Not Tried (Per Cent)
Slight.....	24	45	31
Marked.....	4	74	22

of various factors including toxicity, 27 per cent received no further gold after they had relapsed. Of the remainder (seventy-seven patients) 80 per cent improved again on the administration of gold. If this group is further broken down into those who showed slight and marked improvement with the original course, 95 per cent of those showing marked improvement improved a second time, whereas only 66 per cent of those showing slight improvement, improved again. Thus, if a patient shows marked improvement after the original treatment with gold compound, he will relapse, but will probably improve again on subsequent gold compound therapy. With this in mind, we have now instituted a program of maintenance doses whereby a patient continues to receive gold at regular intervals indefinitely. This is still under trial and no definite schedule has been worked out, but we feel that a severe and disabling relapse can be prevented. At present, after the initial course of gold, we are using a maintenance dosage of 50 mg. every two or three weeks.⁵

The mechanism of the action of gold in the treatment of rheumatoid arthritis is still unknown. Various explanations have been propounded, including the bacteriostatic effect of gold,³ and none are satisfactory. Freyberg⁴ has shown that gold is excreted in the urine in measurable amounts for as long as ten months after cessation of therapy and the median month of relapse for the group is seven months. Thus, it is possible that there is a therapeutic level of tissue gold which must be maintained in order to keep in abeyance the process which is the cause of activity in rheumatoid arthritis.

Psoriasis Associated with Rheumatoid Arthritis. Eight per cent of the 142 patients had accompanying psoriasis.* This group has cer-

tain features which set it apart from the group as a whole. Similarities were the sex distribution (80 per cent females); the age of onset of arthritis (sixteen to forty-one years, with a median of thirty); the duration of the disease (a median duration of three years); and toxic reactions which appeared in four, or 36 per cent. However, dissimilarities were striking. The agglutination with group A hemolytic streptococcus was positive in only one of these 11 cases. The response to therapy was far from satisfactory. One is still well 68 months after the last gold injection. Four, or 36%, showed no improvement, and only 2, or 18%, showed marked improvement. The relapse rate and response to subsequent chrysotherapy were comparable to the group as a whole.

Agglutination with Group A Hemolytic Streptococcus. Since 1931, agglutination with group A hemolytic streptococcus² has been performed in this clinic on sera of all patients with rheumatoid arthritis. In the eight years, 1931 to 1939, under the usual conservative treatment, we had observed a change from positive to negative in only one patient. Since the advent of chrysotherapy in the three and one-half years covered in this report, seventeen patients have changed from positive to negative.

COMMENTS

A representative group of patients with rheumatoid arthritis who have been followed for at least 3 years shows that the disease process can be held in check in a large number by the use of gold compounds. The treatment is attended by a definite number of severe and disabling toxic reactions. That gold is not a curative agent is, we believe, amply demonstrated. There is strong evidence that it influences some system whereby the activity of the disease process is diminished. It is suggested that the excretion of gold is followed by a renaissance of activity of this process. The nature

* The psoriasis antedated the arthritis in six patients, thirteen to three years, a median of six. The arthritis antedated the psoriasis in four patients, four to one years, with a median of two. Psoriasis and arthritis appeared simultaneously in one patient.

of the process is not understood and unfortunately no direct light is thrown upon this problem by the data presented here. However, we do have some indirect evidence. The amount of gold injected is small, an average of 1,250 mg. of the compound, and the response is striking. One may presume that the gold inhibits some active process or system. When the gold is excreted, the system is reactivated to the original state and again can be inhibited by the administration of more gold. The reversibility of the process is therefore its most striking characteristic. In certain patients who showed no improvement, one may postulate that the process had become irreversible and could not be influenced by the action of gold. The patients showing slight improvement were those with the least improvement on subsequent administration of gold, suggesting that, in these patients, the process was tending to become irreversible. Thus a theory can be postulated as to the mechanism of rheumatoid arthritis, namely, that some mechanism is set in motion which can be inactivated by gold, which becomes reactivated when the gold is excreted and which is again inactivated on the subsequent administration of gold. That this mechanism is bacteriological presupposes that the gold exerts a bacteriostatic effect.³ A more satisfying working hypothesis would be that the gold inhibits an enzyme system which becomes reactivated when the gold is excreted.

CONCLUSIONS

1. A group of 142 patients with rheumatoid arthritis treated with gold compounds

has been studied over a period of three to four years.

2. The immediate response to treatment in this group corresponds to that reported elsewhere.

3. The long-term response to therapy is discussed. Eleven per cent showed no improvement, 75 per cent relapsed. Eighty per cent of those who relapsed and were treated again with gold improved again.

4. Rheumatoid arthritis with psoriasis responds less favorably to chrysotherapy than rheumatoid arthritis without psoriasis.

5. A theory for the pathogenesis of rheumatoid arthritis based on the response to gold is suggested.

6. It is believed that patients with rheumatoid arthritis treated with chrysotherapy who show improvement but no toxicity on the first course of therapy should be continued for an indefinite period on a maintenance dosage of gold.

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The Diagnosis and Treatment of Diseases of the Anorectum^{*†}

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HEMORRHOIDS represent varicose dilatations of one or more radicals of the hemorrhoidal plexus of veins. Good results are obtained by the injection treatment provided cases are selected. This form of therapy is indicated only in uncomplicated internal hemorrhoids. The high percentage of recurrence materially further limits its field of usefulness. We respect the fact that a hemorrhoidectomy properly performed is the procedure of choice. Unfortunately, various sequelae are encountered following the surgical removal of hemorrhoids, namely, hemorrhage, immediate and remote, severe pain, anal stenosis, residual infection, abscess formation, fissure and recurrence of the hemorrhoids themselves. The occurrence of such is due largely to the operative technic, lack of knowledge of the anatomy of this portion of the anorectum, the pathologic process itself, unnecessary trauma, failure to preserve adequate anal and perianal skin, inclusion of the sphincter muscle in the clamp and suture and inadequate after-care.

Because of the severe postoperative pain following hemorrhoidectomy, a technic was devised by us which has proved of value, not only toward the avoidance of pain, but

also in the elimination of complications and sequelae.

Under low lumbar analgesia and with the patient in the jackknife position, a retracting speculum is introduced and the pile masses are drawn outside the anus in their respective quadrants. Additional hemostats are applied to the hemorrhoids to bring into view as much tissue as possible without undue tension. If external hemorrhoids are present, a small elliptic incision is made on each hemorrhoid in such a manner that it begins at a point just distal to the anorectal line, and is carried one-half inch beyond the tip of the external pile mass. The skin on either side of the hemorrhoid is elevated with fine forceps and the underlying tissue separated with small, blunt-tipped curved scissors.

The hemorrhoid is elevated and blunt dissection is begun at the apex where the two incisions are joined. The adjacent veins, which have been freed on either side are now drawn medially by an assistant and the operator continues with the blunt dissection on the surface of the external sphincter muscle. When the inner edge of this muscle is encountered, a small right-angle retractor is placed to draw the muscle

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gently from the field of operation. A Smith hemorrhoidal clamp is placed on the internal hemorrhoidal mass in the longitudinal axis of the bowel and the mass cut away. A suture of No. 0 chromic catgut on a small curved needle is introduced one-quarter inch from the tip of the clamp and tied; the free end serves as an anchor. The base of the hemorrhoid is sutured beneath the clamp from side to side and continued to the opposite end of the hemorrhoidal base which lies immediately over the edge of the external sphincter muscle. The clamp is removed as well as the retractor and the muscle permitted to return to its usual location. It is unnecessary to approximate the cut edges resulting from the excision of external hemorrhoids, inasmuch as they fold together nicely as soon as the tonicity of the sphincter is restored.

Immediately on the patient's return to his room, the foot of the bed is elevated for six hours where a hypobaric (light) analgesic solution is used intraspinaly. Liquids, a light soft diet and smoking are permitted. Compresses wrung out in hot boric acid solution are applied continuously. At night these may be supported by a hot water bottle. Morphine sulfate $\frac{1}{4}$ gr. or dilaudid gr. $\frac{1}{20}$ is given only if necessary. The blood pressure in both arms is recorded every hour for six hours. The patient is permitted out of bed the following day. An aqueous solution of 1 per cent gentian violet is applied on a glass rod. Liquid petrolatum is given by mouth once daily for approximately one week. On the second postoperative day, an enema of warm saline or olive oil is administered through a No. 14 soft rubber catheter. Milk of magnesia (one-half to one ounce) is given by mouth daily thereafter. A house diet is prescribed and hot sitz baths thrice daily at a temperature of 110°F. and at a depth of six inches for five minutes are begun.

When discharged on the third or fourth postoperative day, the patient is advised to continue with the sitz baths and employ cotton tissue rather than toilet paper. The lubricated gloved finger is introduced five to seven days from the time of operation.

ABSCESSSES

Anorectal abscesses demand surgical intervention. In the past it has been our custom simply to incise and drain unilateral and bilateral abscesses of the ischiorectal type. Later the fistula was corrected. In an effort to avoid multiple operations and protracted periods of hospitalization and convalescence, an attempt is now made to locate the primary or internal opening at the first sitting. In this type of abscess, the anorectal line is carefully examined, visibly, digitally and by means of a hook, for an ulcer, a crypt or a breach in the continuity of the skin or mucous membrane.

At the maximum point of fluctuation and beyond the outermost border of the external sphincter muscle, a stab wound is made into which a flexible metal probe is gently introduced toward the primary opening. The skin incision is carried to such a point that excision of the fistulous tract is at right angles to the fibers of the external sphincter muscle. The skin over the abscessed cavity is then widely excised to permit adequate drainage. A single strip of vaseline gauze may be placed in the fistulous wound for a period of twenty-four hours. It should be mentioned that for the novice this procedure is not to be recommended. It is better simply to incise and drain the abscess and later remove the fistula. We have performed this maneuver in selected cases in several hundred instances and have seldom encountered a recurrence. Operative wounds are rarely packed and never for more than forty-eight hours. Hot sitz baths are employed thrice daily.

BENIGN GROWTHS

Adenoma and papilloma of the rectum are not uncommon. In our series there have been twenty-nine cases in the young of which nineteen were boys and ten were girls. The ages ranged from fourteen months to eleven years. All lesions were located in the rectum or sigmoid colon. Twenty-one were visualized through the sigmoidoscope, and eight by roentgenologic studies employing opaque enemas and inflation of air. In the adult, these are usually observed during routine examinations but occasionally patients present themselves because of bleeding. With polypoid growths of large size pressure or obstructive symptoms are usual. When biopsy shows no signs of malignancy, destruction by fulguration may be instituted; especially is this true in children. Local excision may be employed in selected cases by a rectal approach. Polypoid lesions in the sigmoid require sigmoidotomy or transcolonic excision. Sessile processes which are usually detected by umbilication of the bowel are best removed by segmental resection.

MALIGNANCIES

Cancer of the rectum and sigmoid represents approximately 80 per cent of all intestinal malignancies. In the male, it is second only to that of the stomach. It is difficult to state accurately whether cancer is on the increase; certainly today this disease process is being observed with greater frequency. There are several reasons that may serve to explain this: first, improvements in diagnostic technic and the more widespread use of these methods; and second, patients are transitioned over the gaps of intermediary illnesses and therefore reach an age when cancer is more common.

A few years ago it was our privilege to review the literature on the incidence of malignancy of the anus, rectum and sigmoid

in youth. One hundred twenty-three authentic cases were found below the age of twenty. Two cases that came under our observation were males. The first, four years and seven months old, had an adenocarcinoma of the rectum. The adenocarcinoma was resected and the patient is well six years following the operation. The second, three years and 8 months of age, had a reticulo-endothelial sarcoma of the rectum which was resected, but the patient succumbed seventeen months later. It seems expedient to state, therefore, that while the majority of cases of rectal and sigmoidal malignancy are encountered between the fortieth and sixtieth years, they may be observed at any age. In fact, we would rather say "there is no cancer age."

There are no pathognomonic symptoms of rectal or sigmoidal malignancy, but there are complaints that are highly suggestive. The passage of blood, bright or dark red in color, occurring at, following or independent of the defecatory act, must be looked upon as a symptom of bowel malignancy until proved otherwise by various diagnostic means. Change in bowel habit, progressive constipation, alternate constipation and diarrhea, early morning diarrhea, incompleteness of evacuation, urgency and frequent desire for stool are suggestive of this dreaded malady.

One must be mindful that approximately 78 per cent of cancers involving the anus, rectum and sigmoid are within reach of the examining finger. Therefore, following a careful history, digital examination is of utmost importance. By proctosigmoidoscopy, with proper cleansing of the bowel, the entire rectum, lower and midsigmoid may be visualized in over 90 per cent of the cases examined. The presence of a fixed, nodular cauliflower-like growth involving the mucosal wall or a deep excavating ulcer with everted edges will serve to make the diagnosis. A biopsy may be made for con-

firmation, and in addition, will disclose the type and grade of tumor.

Where no lesion is demonstrated by careful digital and sigmoidoscopic examination, a roentgenologic study of the bowel, employing an opaque enema, is invaluable.

To cure cancer means early diagnosis and radical extirpation. It is definitely erroneous to assume that a malignant tumor of small size should be eradicated by a conservative operation or that one of large size should be removed by a very radical operation.

The radical one-stage abdominoperineal resection, advocated by Miles in 1907, is still considered by many the procedure par excellence. It permits wide removal of the gland bearing areas, offers a low recurrence rate and a low mortality. It presents one great disadvantage, namely, the establishment of an abdominal colostomy. For this reason alone, innumerable patients jeopardize their lives by refusing what radical surgery might offer. The ingenious procedure designed by Babcock in 1931 permits the same degree of wide excision of the malignant rectum and gland bearing areas with formation of a perineal anus in its normal location. By such, an abdominal colostomy is avoided. Approached through the abdomen and perineum (abdominoperineal proctosigmoidectomy), the cancerous bowel is dissected free and the vascularized sigmoid drawn down to the site of the normal anus. Prior to January 31, 1946, of 430 patients with cancer of the rectum or sigmoid, resection by various means was carried out in 345, a resectability rate of 88.0 per cent. Of this number "proctosigmoidectomy" was performed in 223 instances with fourteen deaths, a mortality of 6.2 per cent. With improvements and refinements in technic, preservation of the sphincter muscle has produced excellent results, in fact in our more recent cases the function may be described as practically that of the normal. The vast majority of

our patients are out of bed on the fifth or sixth day, discharged on the eleventh and return to work six to ten weeks following resection.

PROLAPSE

Except for those cases which present extensive procidentia and prolapse, the condition is seldom recognized, yet it is one of the most frequent entities to be encountered. Any factor, whether anatomic, mechanical or inflammatory, that tends to diminish the normal fascial, muscular or peritoneal supports of the rectum, thereby increasing the motility, is conducive to prolapse and/or procidentia. To one accustomed to the use of the proctosigmoidoscope with the patient in the inverted or knee-shoulder position, varying degrees of mucosal prolapse are easily discernible. Only too frequently these patients offer a history of chronic constipation, an indeterminate type of pressure, a fullness or weight in the pelvis, and incompleteness on evacuation of the bowel. Careful examination discloses complete absence of the normal mucosal pattern, and partial or complete obliteration of the valves of Houston. Marked redundancy and reduplication of the rectal mucosa will be noted by digital examination and through the sigmoidoscope. Not infrequently the condition is associated with redundant sigmoid as evidenced by roentgenographic study following an opaque enema.

In children, prolapse is amenable to injections of quinine and urea hydrochloride or phenol in oil given in $\frac{1}{4}$ cc. dosage circumferentially at graduated levels. In adults, a modification of the procedure, advocated by Murietta in 1938, is ideal. The patient is placed in the inverted position under sacrocaudal or lumbar analgesia, and the prolapse of the anterior wall drawn taut longitudinally and clamped. The prolapse is excised and a running mattress of fine chromic catgut introduced beneath

the clamp. The suture line is inverted by a second catgut stitch. The posterior wall is drawn taut in a transverse fashion. Anchor sutures are placed at the extreme ends and as the prolapsed bowel is excised, clamps are applied to the cut edges of the mucosa. A running mattress of fine chromic is introduced and the resultant line of suture inverted by a second layer. Over 1,000 patients have been operated upon by this method with gratifying results. In this series two cases of hemorrhage and three of stenosis were encountered.

For procidentia, the surgical approach should be abdominal embodying fixation, obliteration and occasionally plication.

CHRONIC ULCERATIVE COLITIS

Chronic ulcerative proctosigmoiditis, described by some as thrombo-ulcerative proctosigmoiditis, is a condition frequently observed. Characterized pathologically by typical changes in the intestinal wall and clinically by its progressive course, the passage of frequent bloody, mucopurulent discharges, tenesmus, abdominal pain, and general lassitude, it is not difficult of diagnosis. One should be mindful that 95 per cent of these cases have their origin in the rectum or lower sigmoid. This, itself, gives evidence of the necessity for proctosigmoidoscopy in routine examination.

Early in the disease, the mucosa exhibits a rather diffuse hyperemia. As the process continues, edema and pitting of the mucosa is apparent. Minute yellowish abscesses may be seen beneath the mucosal layer, which upon rupture form ulcers which give a moth-eaten appearance to the already granular lining of the membrane. In some cases an ironed-out or rounded appearance of the valve edges is discernible. At a later stage, confluence of these petechial ulcerations form large ragged areas. Fever of the septic type is not uncommon, especially during the acute stage, or in exacerbations

of the chronic. Ordinarily the blood count discloses a secondary anemia and a mild leucocytosis. In all these cases it is highly expedient to study the case thoroughly in order to rule out a specific influence. Smears are made by scraping the rectal mucosa and vaccines prepared when pathogenic organisms are found. An opaque enema is administered for the purpose of determining the upper extent of the disease process. In febrile cases, bed rest is imperative. Factors influencing the physical and mental status of the individual are corrected. In fulminating cases, parenteral feeding is employed, otherwise a diet that is of low residue, bland, high in calories, vitamins and proteins, yet low in starch and sugar is prescribed. We have found that frequent small blood transfusions have proved most efficacious. Locally, where the process is confined to the rectum and lower sigmoid, gentian violet, 2 per cent aqueous solution through the sigmoidoscope with insufflation of sulfanilamide has proved advantageous. Retention enemas of olive oil and cod liver oil may be judiciously used. For diarrhea, kaomagma, kaopectate by rectum and by mouth is usually satisfactory. A mixture of bismuth subcarbonate $\mathfrak{3i}$ in warm olive oil $\mathfrak{3iv}$ by rectum three or four times daily is beneficial.

Vitamin therapy has proven to play a most important part in the melioration of this condition. Vitamin A, 100,000 units intramuscularly, vitamin B complex, containing thiamin chloride 20 mg., nicotinamide 150 mg., riboflavin mg. 4, pantothenic acid mg. 5, pyridoxine mg. 10, twice daily. Sodium ascorbate 500 mg. daily is administered intravenously. This is continued during the period of hospitalization. We have observed beneficial results with neoprontosil, gr. 5, every six hours for ten days. Sulfathalidine has been employed in forty-seven cases; there were four reactions; improvement was observed

in thirty-five patients; twelve showed no benefit.

PRURITUS ANI

Pruritus ani is a syndrome embodying an alteration in the anal and perianal skin, due to irritation in the peripheral nerve endings, caused by some local or systemic disease. The chief symptom is itching, which is characterized by its chronicity, rebelliousness to treatment and tendency to recurrence.

So long as there is no one specific cause of pruritus, just so long will there be no specific treatment. Much has been written and suggested for this distressing malady, and while the treatments have been worrisome and frequently unsatisfactory, the chief purpose in following any procedure is to allay the distress while attempting to seek the cause. The examination should be thorough and untiring, using every available means to find some influencing factor. Should any anorectal disorder be discovered, it must be corrected. Invariably, where such a pathological condition exists, its removal will result in definite improvement. Cleanliness is essential and may be accomplished by washing the anus and surrounding areas with warm water and castile soap twice daily and after defecation. Absorbent cotton is preferable to any toilet paper now in use. Irritations from tight clothing, tending to rub the anal skin, should be avoided.

Importance of the dietary régime should not be underestimated; not only are certain foods irritating of themselves, but the manner in which even bland foods are prepared and seasoned may render them unsuitable. Green vegetables, especially spinach, peas and carrots, are permitted, as well as potatoes, milk, cereals and fruits, both fresh and stewed. Fowl and moderate amounts of unseasoned red meat may be taken. Water should be consumed liberally. Such foods as oatmeal, salt fish, oysters, clams,

crabs, lobsters, cheese, pickles and cucumbers are interdicted. Excessive eating, the use of condiments, and overindulgence in alcohol are to be avoided, as well as a superabundance of seasoning.

Inquiry as to the general health and habits of the individual should be made. Fresh air, sunshine and rest are advocated for an impaired general condition. Tonics of iron, phosphorus, arsenic and cod liver oil may aid generally in improving the health.

It has been shown that nervous irritability in these cases should not be minimized, and for this potassium bromide, 5 to 10 gr., or phenobarbital, either the sodium salt, $\frac{1}{4}$ gr., or the elixir, $\frac{1}{2}$ to 1 dr. is given every three hours for a few days.

Insomnia may be relieved by the use of one of the barbiturates, as luminal, 1 to 2 gr., nembutal, 3 gr., or bromide, 10 to 20 gr., using either the sodium or strontium salt. The opiates are interdicted.

Sluggish intestinal evacuations may be corrected by the use of one of the following given once or twice daily as necessary: Cascara sagrada, $\frac{1}{2}$ to 1 dr., magnesium sulfate, $\frac{1}{2}$ to 2 dr., liquid petrolatum, $\frac{1}{2}$ to 1 ounce; or enemas of plain hot water, salt water, or warm olive oil. As an intestinal antiseptic, the sulfocarbolate of zinc, 5 gr. every two hours, is advocated after proper bowel function has been restored.

Associated anorectal disorders, such as hemorrhoids, fistulas, cryptitis, papillitis, condylomas, skin tags, proctitis, etc., should be corrected. Helminths, as pin or threadworms (*oxyuris vermicularis*) may be destroyed by use of santonin, 1 to 3 gr., or calomel, 2 gr. given for three successive nights. Where fungi have been demonstrated, the administration of potassium iodide, saturated solution, beginning with 20 drops thrice daily and increasing one drop until the symptoms of iodism appear, is recommended. Thereafter, the dosage is

decreased slightly and continued for several weeks. Many patients improve upon reaching the saturation point and remain symptomatically free for varying periods of time. Whitfield's ointment and Deek's ointment (salicylic acid, 4 per cent, mercury salicylate, 4 per cent, oil of eucalyptus, bismuth subnitrate, 10 per cent, in a mixture of equal parts of lanolin and petrolatum) are of value. Rectal irrigations of lime water, quinine bisulfate, 1:2000, infusion of quassia, 5 per cent; saline solution (1 ounce to 1 pint of water), acetic acid, $\frac{1}{4}$ to 1 per cent solution, and turpentine or benzine may be instituted.

Dermatologic conditions, such as eczema marginatum and tinea trichophytina, may be eradicated by salicylic acid, 10 to 15 gr., to 1 ounce of petrolatum; crude coal tar, $\frac{1}{2}$ dr. to 1 ounce, liquor detergens, $\frac{1}{2}$ dram to 1 ounce; or the following:

R
Iodi..... gr. xx
Potassi iodidi..... gr. xl
Acidi salicylici..... gr. xlv
Acidi borici..... ʒ iss
Alcoholis..... ʒ iii
(50%)..... q.s.fl.)
M. et ft. solutio.
Sig.—Apply locally and allow to dry.

In mild pruritus, the following may be used:

R
Phenolis..... gr. x
Lotio calaminae, q.s.fl..... ʒ iii

R
Acetanilidi..... ʒ i
Petrolati..... q.s. ʒ i
M. et ft. unguentum.

In some cases, citrine or chloroform ointment will allay the itching. If the area is moist, dusting powders, as zinc stearate or calomel, may be used. The following is recommended:

R
Dithymol-diiodidi..... ʒ i
Bismuthi subcarbonatis..... ʒ iii
M. et ft. pulv.

The skin should be washed with warm water and castile soap and dried before

the powder is applied. If the skin is thick and leathery, mercury, phenol, 1 to 5 per cent in lotion or ointment form and silver nitrate, 1 to 15 per cent are stimulating. Potassium permanganate, saturated solution ($29\frac{1}{2}$ gr. in 1 ounce water), may be painted over the surface daily. Liquor potassae, solution of mercuric chloride or a 10 per cent nitrate of mercury ointment have proved of value. If the skin is acutely inflamed, calomel and lime water may be applied:

R
Hydrarg. Chlor. mitis..... gr. xvi
Liquor calcis..... q.s. ʒ iv

Cracks, fissures, and excoriations may be treated by topical applications, using a glass rod or stick, of (1) phenol, 90 per cent solution, neutralized by tincture of benzoin; (2) silver nitrate, 10 to 20 per cent solution or stick, neutralized by tincture of iodine; (3) silver nitrate, 50 per cent solution, used alternately with citrine ointment; (4) pure ichthyol; or the following:

R
Phenolis..... gr. xx
Acidi salicylici..... ʒ i
Camphorae..... gr. v
Glycerini..... q.s.fl. ʒ i
M. et ft. solutio.
Sig.—Apply locally.

Following the use of the foregoing prescription, when excoriations are healed, tincture benzoin may be applied, or the following:

R
Balsami peruciani
Olei ricini..... aa fl. ʒ i

In all cases, it is advisable to make a smear of the anal and perianal skin preferably by means of a cellophane glass rod. Culture of the organisms and subsequent injections may effect a cure.

Recently decided benefit has been obtained for patients with pruritus by regulating the hydrogen ion concentration of the surface of the rectal mucosa. In pruritus the

concentration is usually above 7.5. After the administration of an acid-ash diet and a capsule of glutamic acid, hydrochloride gr. 5 and pepsin gr. 1 with each meal, the hydrogen ion concentration is lowered and the symptoms abate in the majority of the cases. In the more refractory patients, it has been found advantageous to employ a nightly retention enema of 2 ounces of lactic acid (2½ per cent solution) in a pint of water. With this form of therapy, other methods of treatment, particularly those contributing to cleanliness, are combined.

Injection Methods. As is well known, alcohol possesses a destructive effect on the nerve structures and for this reason has been employed in the treatment of pruritus ani. Stone advocated the subcutaneous injection of 95 per cent grain alcohol to destroy the terminal sensory filaments that supply the diseased area. In a few hundred instances we have employed varying strengths and amounts of alcohol and although many sequelae have been encountered such as abscess, necessitating free incision and drainage on one or more occasions, as well as a protracted convalescence, our conclusions are that it is an excellent means toward the eradication of this distressing syndrome. Under sacrocaudal or sodium pentothal anesthesia, the parts are thoroughly prepared, and 40 to 60 cc. of alcohol 47.5 per cent are injected subcutaneously around the sphincter muscle. Other preparations and solutions such as hydrochloric acid, benacol, distilled water, quinine and urea hydrochloric and anucaine, may be employed.

The hypothesis of Besredka as applied to the pruritic syndrome entails the taking of cultures from the anal and perianal region of patients suffering from pruritus. The débris or scrapings before and after sterilization are planted in hormone broth and incubated at 37.5°C. for seventy-two hours. After identification of the organisms, the

culture is passed through the Berkefeld filter and the antigen completed by the addition of 3 drops of tricresol 0.1 per cent solution as a preservative. The prepared autogenous vaccine is injected intradermally and subcutaneously into the pruritic area after cleansing of the surface with alcohol. Initially 5 to 6 minims is introduced and the dose gradually increased until 16 minims (1 cc.) are given. Injections are given every third day. Two to four areas are treated at each sitting. The writers instituted this treatment a few years ago as previously reported.

The value of surgery in the treatment of pruritus ani is indeed problematic. Certainly it should be resorted to only after co-existing disorders have been corrected and at least one or even two forms of the injection treatment have been given a fair trial. The operative means of combatting pruritus ani confines itself to (1) the removal of the diseased skin; (2) severance of the sensory nerve filament supplying that skin; and (3) division of the peripheral nerves following their identification by means of a faradic current.

PILONIDAL CYSTS

Pilonidal cysts and sinuses are encountered with comparative frequency. Pain and discomfort of varying degree, swellings and mucopurulent discharge with incision and drainage on one or more occasions, are usually cited by the patient. Examination discloses one or more openings in the midline or adjacent skin overlying the sacrococcygeal region. An inflammatory process presenting increased heat, swelling, tenderness, induration redness and fluctuation, with pus discharging from the opening and perhaps a tuft of hair extending therefrom, leaves little doubt as to the diagnosis.

The treatment is distinctly a surgical one and consists of the removal of the cyst and all tributary tracts. The relative merit of

closing or permitting the resultant wound to heal and fill in by granulation is and probably always will be a moot question. Over the ten-year period ending 1938, a series of 414 operative cases were studied in the proctologic clinics of the Graduate and Temple University hospitals. Conclusions drawn from this survey have established rather definite criteria for both the open and the closed methods.

Pilonidal cysts and sinuses presenting acute abscess formation, and/or multiple tracts and openings and/or definite involvement of the sacrum or coccyx, are best excised in their entirety and left open to granulate in from the bottom. Recurrent cases fall in this category also. Conversely, pilonidal cysts and sinuses of small or moderate size presenting congenital mid-line openings, and devoid of an acute inflammatory process with abscess formation may be sutured. In the latter, as in all cases, all existing pathological conditions must be removed, hemostasis complete and all dead spaces obliterated. For closure, interrupted sutures of No. 32 alloy steel wire placed in tier formation are introduced until the skin is reached. The skin itself is not approximated. From 1938 until the present, 154 private patients have been treated by the above criteria. All have been followed carefully. In seventy of the 154 cases, the average period of hospitalization was three and three-fourths days; the average period from the date of operation until complete healing was noted as thirty-nine days or approximately five and one-half weeks.

LYMPHOGRANULOMA

Probably the most fascinating disease entity drawn to our attention during the past decade and a half is lymphogranuloma inguinal or lymphopathia venereum. To us, it is of special interest by virtue of the fact that inflammatory stricture of the rectum, and esthiomene of the anoperineal

and anovulvar region, are most frequently due to the filterable virus of lymphogranuloma venereum. Stricture of the rectum is an organic narrowing of the lumen of the bowel by fibrous tissue involving the mucous membrane, submucosa and muscular coat. It is characterized by progressive constipation, tenesmus and mucopurulent discharge. Rectal manifestations are more common in the female because of the distribution of the lymphatic network. The condition is more frequent between the ages of seventeen to forty, or the period of greatest sexual activity. Also there is a marked preference for the colored race. In our series were 1,124 cases, 729 of which were negroes.

It should be borne in mind that the inflammatory process may attack any layer of the rectum or the tissues outside its wall. If from within, the irritation results in erosion of the mucous membrane, upon which infection is superimposed. With continuation of the etiologic irritant, the inflammatory process becomes subacute and finally chronic in nature, so that the various layers of the rectum and tissues outside its wall are gradually involved by continuity and contiguity of structure. As a result of this chronic inflammation, much young fibroblastic tissue is deposited in the submucosa as well as in the other coats, which gradually leads to thickening of the visceral wall. This in itself tends to encroach on the lumen of the rectum. By subsequent contraction of the maturing fibroblastic tissue this thickening becomes markedly increased, so that there eventually results a firm, inelastic, permanent narrowing, to which the term stricture is applied.

On the other hand, if the initial focus is outside the rectum, as the writer believes is more frequently the case, the extramural network of lymphatics becomes invaded. As the inflammatory process gradually becomes chronic, the mural tributaries, i.e., the intermural and intramural groups, are

invaded by extension. As a result of the inflammatory process, fibrous tissue is deposited in the various layers of the rectum so that thickening occurs which brings about narrowing of its lumen. As the process continues and additional fibroblastic tissue is deposited, subsequent contraction ensues, so that finally an organic stricture is formed. Erosions of the mucous membrane are noted, followed by ulcerations, and the surrounding mucosa appears altered and somewhat lusterless. To the touch, the involved area is thick and firm, while later it feels leathery with loss of elasticity and distensibility. It is more or less irregular, markedly thickened, and the mucous membrane is found to be adherent to the tissue beneath. In the deeper layers of the stricture, fibrous tissue is seen involving all the coats of the rectum, although the greatest amount of involvement is in the submucosa. Fistulous tracts may be found passing through the perirectal tissues to adjacent structures, as the bladder, urethra, vagina or through the skin. Ulceration is usually marked and occurs early. The discharge is frequently abundant, mucopurulent and often sanguineous. Ulceration rarely exists at the level of the stricture except in the tubular variety, which is seen routinely through the stricturoscope and at autopsy.

A history of constant soiling by feces, blood and pus is suggestive of an inflammatory stricture, especially when cited by a colored female between the ages of twenty and forty. Although the diagnosis by inspection is not absolute, it offers to the careful observer a very good idea of the pathological condition present. Not infrequently, the region about the anus is moist and glued together by the thick mucopurulent discharge. Upon separation of the buttocks, fecal matter mixed with blood and pus may be seen seeping through the anal orifice. Hypertrophied skin tags, condylomas of various sizes, and one or more fistulous

openings are not uncommon. Since approximately all inflammatory strictures of the rectum are within reach of the finger, the diagnosis should not be difficult. As the gloved finger is inserted into the anal canal, some degree of muscular relaxation will be noted in long-standing cases, due to fatigue of the external sphincter, yet gentleness should attend this procedure, since pain and discomfort are not unusual. As the finger is advanced the stricture will be felt as a firm inelastic narrowing, usually involving the entire circumference of the rectum. If the lumen of the stricture is of sufficient size to admit the tip of the index finger, the finger usually can be passed to its entire length. However, such introduction should be attended by great care, since forcible insertion not only causes pain but is dangerous, because the diseased tissue is so friable that hemorrhage and perforation may ensue. Through an ordinary proctoscope the stricture, or, in the case of the tubular variety, the lower border of the stricture, is noted by its pale, leathery, and thickened appearance. In each case, especially if the stricture is located in the sigmoid or at a high level in the rectum, roentgenograms should be taken after an opaque enema.

In 1925, Frei, of Berlin, introduced a cutaneous test for this disease which has proved of distinct diagnostic value in inguinal adenopathies and anorectal syndromes. More recently we have employed the chick embryo antigen (Lygranum) and have found it more specific. Use is made of yolk sacs harnessed from chick embryos moribund or recently dead from infection with the agent of lymphogranuloma venereum and containing the agent in high concentration free from contamination with other micro-organisms or viruses. The technic for testing patients diagnostically is the same for both antigen and antigen control. After preparing the skin of the fore-

arm with alcohol, 0.1 cc. of each material is inoculated intradermally into the forearm and the reaction is read at forty-eight and seventy-two hours by measuring the diameter of the resulting papules. A papule 6 by 6 mm. or greater indicates a positive reaction providing the papule produced by the antigen control is 5 by 5 or smaller. Of twenty-four intradermal tests, twenty-two positive reactions were observed which were confirmed by clinical and histopathologic study.

In every case effort must be made to ascertain the cause and any influencing factor in order that treatment may be instituted accordingly. For instance, if syphilis co-exists, proper antiluetic treatment should be given even though it has no effect on the fibrotic stricture; if the patient is tuberculous, measures should be directed thereto. Attempt should be made to build up the constitution of the patient, since there are usually varying degrees of weakness and loss of weight. The diet should be nutritious and composed of foods which leave little residue. Ordinarily a low residue diet in four feedings is composed of protein 120 Gm., carbohydrates 400 Gm. and fats 50 Gm., supplemented with amino acids 15 per cent solution. Instillations of ichthyol, 2½ to 5 dr. (10 to 20 cc.) of a 25 per cent aqueous solution twice daily are soothing to the mucous membrane and will assist in diminishing tenesmus.

Perineal excision preceded by a permanent colostomy is applicable for all variations of stricture of the rectum. The procedure recommends itself because it is not so formidable as other types of excision, and irrigations through the distal colostomy loop may be instituted. Fifty-one such operations (Lockhart-Mummery technic) have been performed by one of us (H. E. B.) with one death (1.9 per cent), twenty-four of which were previously reported. A number of abdominoperineal extirpation (Miles

technic) have likewise been done with one death. Negroes, are loath to accept an abdominal stoma because of their age group and their type of occupation so that in their race, too, we have found it desirable to perform an abdominoperineal resection (proctosigmoidectomy) without colostomy and with preservation of the sphincter musculature. This technic has been employed in nineteen patients; and while convalescent period in some instances was quite protracted, there were no deaths. Of course, in the presence of pararectal abscesses and fistulas with free suppuration, incision and drainage is indicated followed later preferably by a two-stage interval resection. Preliminary x-ray therapy was used in a small series of cases for the purpose of demonstrating the size of infection; the results were highly satisfactory.

ANAL STENOSIS

During the past few years many cases of anal stenosis have been observed usually as the result of removing "too much skin" at the time of operation. In our operations for cancer "proctosigmoidectomy" where the sigmoid is drawn through the anal orifice, we have experienced more than an occasional case of narrowing at the junction, so that an ample opportunity to employ various technics for correction has been afforded. The method devised by Martin of Detroit has proved of special value and has been utilized in over 250 cases without a single failure. The technic is simple and consists of mobilizing a small portion of the mucous membrane immediately above the stenotic area and preferably in the posterior phase. A slit through the stenosis in this site is made following which the mobilized mucous membrane is tacked to the marginal wound with two or three interrupted sutures of chromic catgut. Subsequent dilatation has at no time been necessary.

Seminar on Antibiotics

Penicillin Aerosol and Negative Pressure in the Treatment of Sinusitis*

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THE physiologic basis for the use of penicillin aerosol and negative pressure in sinusitis may be stated as follows: A negative pressure of approximately 60 mm. Hg is intermittently produced in the sinuses during the inhalation of a fine mist of penicillin. Air withdrawn from the sinuses during the suction cycle is replaced by penicillin aerosol when the pressure in the nose becomes positive. Aeration and drainage of the paranasal cavities, with deposition of penicillin on the mucous membrane, follows this procedure unless the orifices to the sinuses are completely obstructed.

In earlier studies on nasal inhalation of penicillin aerosol beneficial results were at times observed in patients with sinus infections.¹⁻⁴ More favorable reports from inhalation of penicillin through the nose at atmospheric pressure have appeared, notably that of Vermilye.⁵ Although ventilation of the sinuses takes place in some instances during normal breathing by the slight negative pressure in inspiration producing a venturi effect in the orifices that lead to the paranasal sinuses, a more efficient ventilation of these cavities was achieved by creating a negative pressure

of 50 to 70 mm. Hg in the nasal passages with immediate replacement of the air withdrawn by penicillin aerosol.⁶ The apparatus devised for this purpose and a report of its clinical effect in acute and chronic sinusitis indicated that this procedure had therapeutic value.^{6,7}

The antibiotic effect of penicillin depends on the entrance of the nebulin of this drug in sufficient concentration to result in bacteriostasis and on the presence of penicillin sensitive organisms in the sinuses. Previous experience with oral inhalation of penicillin in bronchiectasis and other bronchopulmonary infections has revealed the specific value of aerosol therapy in patients with infections caused by pneumococci, hemolytic streptococci and *Staphylococcus aureus*.^{1,2,5,7,8,9} At times improvement has been obtained in patients with bronchial infection due to *Streptococcus viridans*. Penicillin is known to be effective locally in high dilutions and has the advantage over chemotherapeutic sulfonamide aerosols previously used¹⁰⁻¹⁴ in that this newer antibiotic is not inactivated by purulent exudates or para-aminobenzoic acid.

In cases of mixed infection, however, a favorable response to penicillin therapy

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frequently does not take place. This may be due to the pathogenic character of the organism, such as the colon bacillus, or it may be due to gram-negative bacteria which produce an enzyme that nullifies the bacteriostatic effect of penicillin, as Abraham and Chain¹⁵ first pointed out. The enzymatic nature of "penicillinase" has been substantiated by Woodruff and Foster.¹⁶ Meleney¹⁷ has also recently demonstrated that para-chloralphenol is effective against gram-negative organisms and that when it is used in surgical mixed infections results in a marked increase in the clinical effectiveness of penicillin. In the first report on inhalation of penicillin aerosol in bronchopulmonary disease¹ it was noted that the gram-positive organisms were generally absent in the sputum culture after effective therapy and that gram-negative organisms were then found on culture, especially *Bacillus aerogenes*, *pyocyaneus*, *proteus* and coliform organisms. Our belief was that these organisms that appeared subsequent to treatment grew out more easily following the disappearance of gram-positive bacteria. Although gram-negative bacteria may not in themselves be pathogenic, the growth of these bacteria may at times prevent the beneficial activity of penicillin by the "penicillinase" mechanism referred to above. Recent experience in our clinic has tended to confirm this point of view.

In a series of seventy-five patients with bronchiectasis treated by Olsen¹⁸ 50 per cent were found to be resistant to this drug and 50 per cent showed marked improvement. In eleven patients whose response has been poor, the addition of streptomycin aerosol resulted in the disappearance of the gram-negative organisms and conspicuous reduction in the volume and purulent character of the sputum with corresponding clinical benefit. The striking cures obtained by Segal¹⁹ in pneumococcus lobar pneu-

monia reveal the effectiveness of penicillin aerosol in a single infection with a sensitive organism. Although mixed infections, such as are found in lung abscess as well as chronic pulmonary disease, are at times markedly benefited by penicillin aerosol,^{1,19} the newer findings on the significance of gram-negative organisms has encouraged the investigation of streptomycin aerosol as well as para-chloralphenol and sulfacetamide to be used in combination with penicillin. In requesting sputum cultures it seems important now to ask for the list of organisms present, especially the occurrence of gram-negative organisms. The bacteriology of all the micro-organisms found in a sputum would require a large amount of careful work and may not always be feasible. However, the presence of organisms which have a gram-negative stain should be noted in the report, even if the exact nature of the bacteria may not be completely worked out.

The antibiotic effect of penicillin nebulin introduced in the sinuses cannot be entirely separated from the effect of negative pressure itself, in that better aeration and drainage might be of therapeutic value in itself. The value of reduced atmospheric pressure in a low pressure chamber was reported by Andrews, Roth and Ivy²⁰ in the treatment of paranasal sinusitis. However, the employment of negative pressure itself in the sinuses without an antibiotic might result in secretions entering uninfected sinuses without the protection of a drug that will act to inhibit bacterial growth. In the cases previously reported as well as the present series no instance of an infection of an uninfected sinus cavity has been observed when penicillin aerosol was used in conjunction with intermittent negative pressure.

METHODS

The apparatus originally described⁶ included a nebulizer with a rebreathing bag and cone-shaped glass nosepieces for nasal

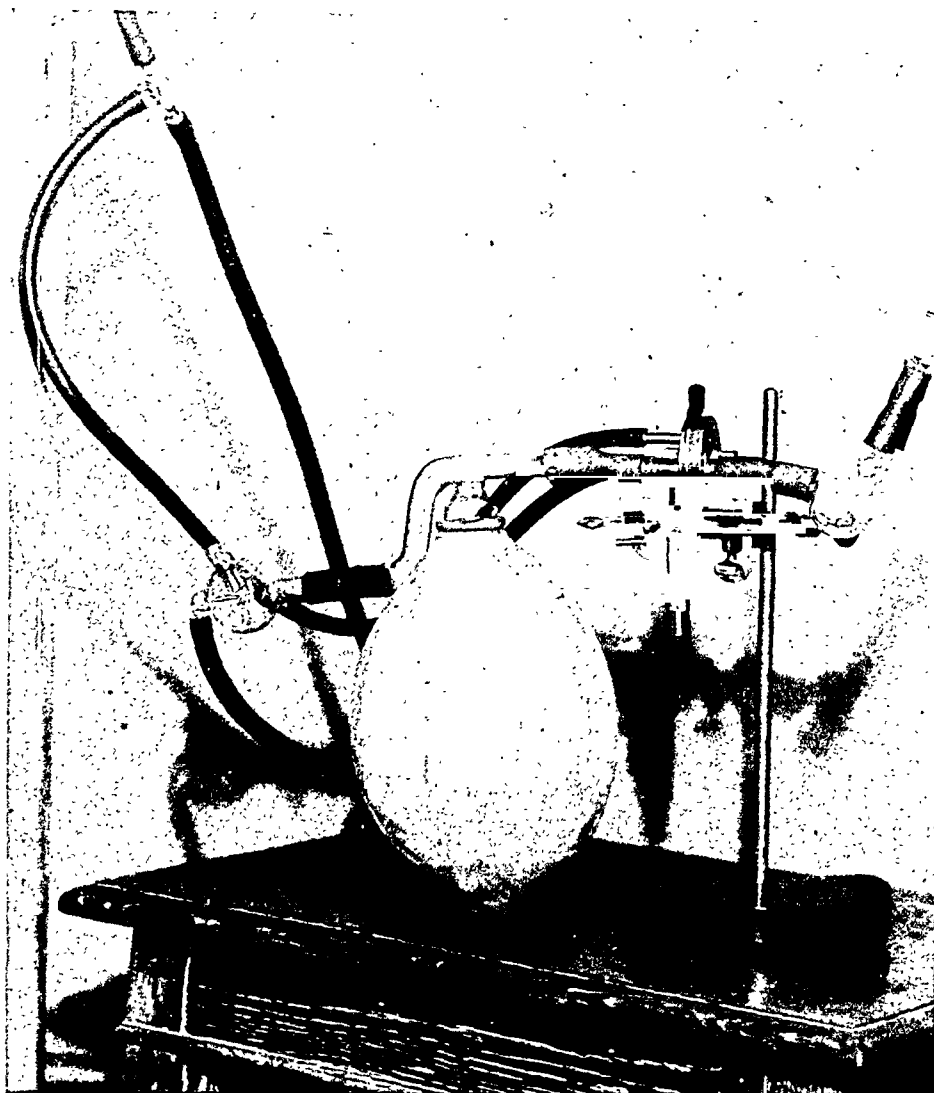


FIG. 1. *Apparatus for penicillin aerosol with rebreathing and negative pressure.*

inhalation of penicillin. A glass venturi tube inserted in the rubber tubing from the oxygen cylinder was used for the production of positive pressure by oxygen flowing through the distal end and for negative pressure through the side arm. A specially constructed valve connected the nebulizer to positive pressure when its handle was upright and to negative pressure when it was turned downward. The patient begins by taking three breaths of penicillin mist; the handle of the sinus valve is turned downward and he is then instructed to swallow. In this position the patient is connected with the side arm of the venturi and a negative pressure of 50 or 60 or more mm. Hg is produced, depending upon the flow of oxygen from the regulator. When the nasopharynx is closed a suction effect within

the nasal passages is experienced by the patient and the nose is drawn inward; the handle of the valve is turned upward, oxygen passes through the nebulizer and inhalation of penicillin aerosol takes place again for three breaths.* (Fig. 1.)

In a more recently developed apparatus negative pressure and a slight positive pressure is used. (Fig. 2.)† Penicillin is produced during the phase of positive pressure and enters the nose while the patient breaths partly through the nose and partly through the mouth. The rebreathing bag is eliminated. After three breaths the valve is turned downward, the patient is instructed

* The apparatus is made by Mr. F. F. Anderson, 4652 Spuyten Duyvil Parkway, Bronx, 63, New York.

† This apparatus is manufactured by the Oxygen Equipment Mfg. Co., 405 E. 62nd Street, New York City.

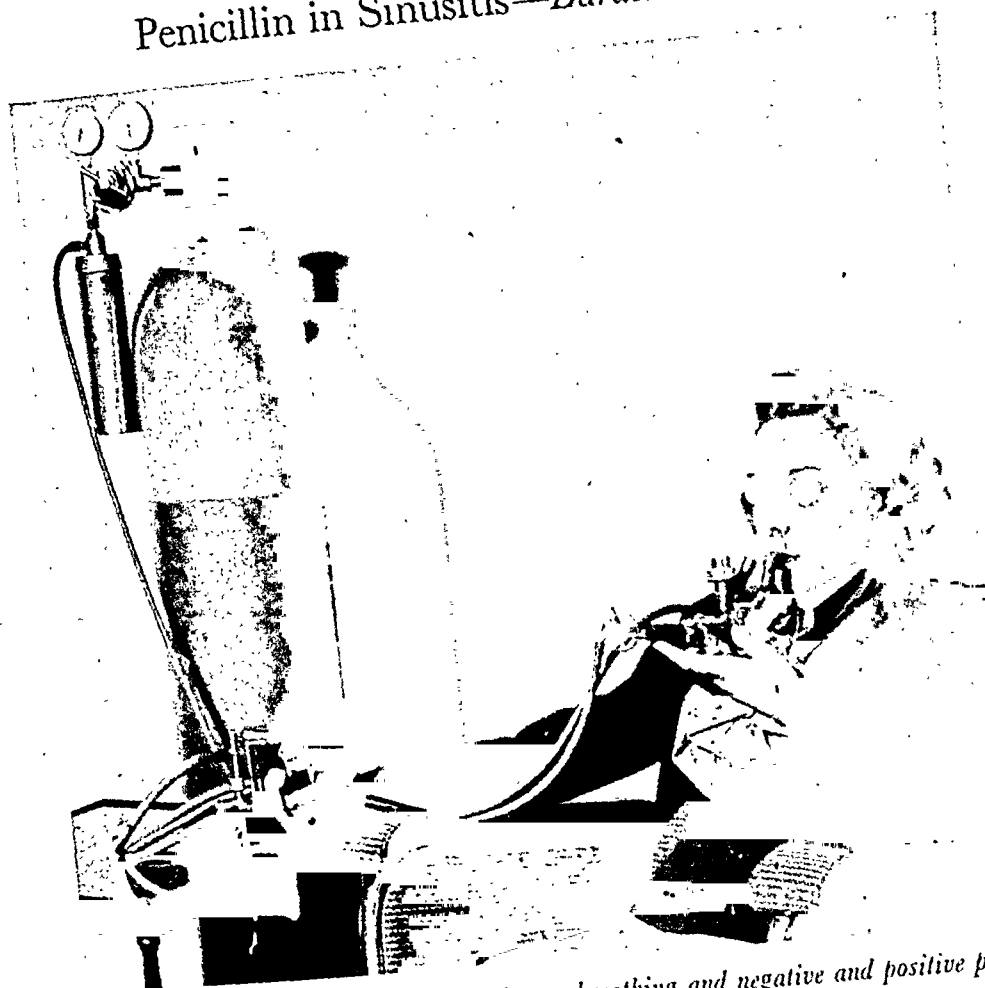


FIG. 2. Apparatus for penicillin aerosol without rebreathing and negative and positive pressure.

to swallow and as soon as the experience of suction is felt, the valve handle is turned upward and the patient is then told to exhale through his nose. An expiratory valve which opens at a pressure of 20 mm. Hg is set in a glass trap designed for the collection of secretions that may be sucked from the nasal passages and sinuses. When the patient exhales through his nose a moderate positive pressure is maintained by oxygen which carries a relatively dense mist of penicillin aerosol. In the positive phase the patient does not swallow and pressure on the Eustachian tube is thus everted. Since higher pressures than 20 mm. Hg were occasionally uncomfortable, the valve has been set to give this pressure. Penicillin may then be introduced into the sinuses when the negative phase is terminated by atmospheric pressure and also during the positive cycle. After the patient has exhaled through the nose three breaths are again taken in order to fill the nasal passage with

penicillin mist and the procedure is repeated.

The use of penicillin aerosol is at times followed by soreness and redness of the tongue or by a black coating on the tongue. It was previously found from studies on the oral administration of penicillin in water²¹ that the tongue not infrequently showed the characteristic changes mentioned above. This took place to a lesser extent when the mouth was washed immediately after ingestion of penicillin solution. Evidence is not at hand to explain the precise cause of sensitiveness of the tongue to penicillin, either in solution or in aerosol form, but it seems to be definitely related to the local effect of penicillin.

Elimination of the larger sized particles in penicillin aerosol was tried to avoid this complication by connecting a baffle to the Vaponefrin nebulizer on which larger particles would be precipitated, and then washed back into the nebulizer and re-used,

and by the construction of a nebulizer in which small particles were more consistently produced. In addition, it was found more comfortable for the patient who inhaled penicillin orally to humidify the aerosol by placing hot water in the rebreathing bag and by having the rubber bag itself placed in a container of hot or boiling water. In the sinusitis apparatus the technic has been changed recently to include the instillation of hot water into the glass trap connected to the nose pieces. Although the nasal mucous membrane itself generally shows no signs of irritation with the inhalation of 50,000 units of calcium or crystalline penicillin per cc., exhalation of the mist over the tongue without the precautions mentioned above has at times resulted in either reddening of the tongue or the development of a black deposit on its surface. Studies are in progress to determine the effect of the two modifications mentioned above: (1) the use of a small particle size aerosol and (2) humidification of the aerosol prior to entering the nose and mouth. When the rebreathing bag is punctured by a hole $\frac{1}{4}$ inch in diameter, the excess oxygen and aerosol is eliminated. In the apparatus without the rebreathing bag the aerosol is exhaled through the nose. The cause of the red or black tongue does not appear to be related to the concentration of the aerosol since it develops when penicillin is swallowed in solution with a concentration of 500 units per cc. Whether this transient complication will occur with crystalline penicillin remains to be seen; if it is due to a change in bacterial flora, the main remedy to avert it may be rinsing the mouth with water after each inhalation. A marked variation in individual susceptibility has been manifested since some patients have no such reaction after months of therapy and others will develop it in three days.

In cases of chronic sinusitis treated in the hospital, or at home, the customary pro-

cedure has been the nasal inhalation of 50,000 units of penicillin aerosol in 1 cc. of saline with negative pressure four times a day. In a few cases penicillin has been given systemically before retiring, either orally or by injection. In some patients with acute sinusitis, or with an acute exacerbation of a chronic sinusitis, a single treatment a day has been employed for a period of three days to two weeks. The indications for the frequency and length of treatment cannot be concisely outlined at this time, but in general it may be said that patients with chronic disease are more apt to require three or four treatments a day.

EXPERIMENTAL RESULTS

Experiments were conducted to determine the pressures in the nasal passages and in the antrum during the negative phase of the treatment. Two patients who had persistent oral-antral fistulas following extraction of upper molar teeth were used as subjects.* A catheter attached to a mercury manometer was passed from the mouth into the antrum. Pressure readings for the nasal passages were obtained by connecting a mercury manometer to the glass nose piece. Pressure readings from a typical experiment were as follows:

Oxygen Flow Liters Per Minute	Pressures in Mm. Hg below Atmospheric	
	In Nasal Passages	In Antrum
3	22	20
4	40	36
5	60	52
6	90	64
7	148	65
8	156	69

The pressures within the antrum follow closely the pressures within the nasal pas-

* These volunteers were obtained through the cooperation of Dr. Morris Hickey of the School of Dentistry.

ages at oxygen flows of 5 liters per minute or below. At higher rates of flow negative pressure within the antrum reach a plateau and then do not materially increase. When the negative pressure in the nasal passages is excessively high the mucous membrane surrounding the ostium may be sucked in and occlude the opening. In some cases when the suction in the nasal passages was released and the pressure in the nasal passages became atmospheric, a negative pressure of approximately 60 mm. Hg would persist in the antrum, dropping suddenly after ten or fifteen seconds. This would confirm the view that the ostium may be temporarily occluded by too high negative pressure.

The subjects with oral-antral fistulas were also used in experiments conducted to determine the amount of penicillin reaching the antrum during the treatment. Following a treatment with 50,000 units of penicillin aerosol administered with the alternating pressure apparatus, 7.5 cc. normal saline was introduced into the antrum through the catheter and withdrawn a few minutes later. Amounts of penicillin recovered varied from traces to 70 units. These figures were found to represent only a portion of the penicillin present; the remainder being absorbed or clinging to the mucous membrane. Thus, when 5,000 units of penicillin in 5 cc. saline were introduced through the catheter only 376 units could be recovered twenty minutes later, approximately 7 per cent of the amount instilled.

A second group of experiments was carried out to determine whether penicillin entered the antrum only in the form of an aerosol or whether the mist was deposited on the walls of the nasal cavity, including the external opening of the ostium, and sucked into the sinus in the form of a liquid during the phase following the release of suction.

A subject was instructed to take three

inhalations of an aerosol containing 50,000 units of calcium penicillin in 1 cc. normal saline. The nosepieces were removed and he inhaled three times through his nose and out his mouth; the nose pieces were replaced and suction was applied. The degree of negative pressure obtained in the antrum was measured by attaching the rubber catheter to a mercury manometer, and averaged 80 mm. Hg. The nose pieces were then removed until the manometer reached the zero mark and the cycle repeated sixty times. At the termination of this procedure, which required about thirty minutes for completion, the antrum was washed with three 8 cc. portions of normal saline. These portions were pooled and an assay made for penicillin content. In one experiment 16 to 20 units of penicillin were recovered; in a second 2 to 3 units.

Penicillin may have lodged on the mucous membrane of the nasal passage near the sinus opening and then sucked inside the sinus during the negative pressure cycles.

The inspiration of penicillin aerosol may also have created a venturi effect on the sinus opening and although expiration was through the mouth, traces of penicillin may have drawn into the sinus during succeeding inspirations of aerosol.

A third group of experiments was conducted in order to determine whether or not an aerosol could be expected to deposit on the walls of a sinus if the mist entered the cavity. A nebulizer was connected to a 2 by two inch diameter rubber tube 35 cm. long. A 10 cc. syringe with piston removed was attached to the other end. The syringe was filled with penicillin aerosol (concentration 50,000 units per cc.) and the contained mist then injected into a rubber catheter immersed in a 25 cc. glass graduate containing glass beads and filled with water. The procedure was repeated forty-five times and the contents assayed for penicillin. Following this the same procedure was

employed but with the catheter in the subject's antrum. After the completion of the procedure the antrum was washed as previously described. These results are seen in Table I.

TABLE I

Date	Interval after Completion of Procedure before Sinus Washed	Total Units of Penicillin Recovered
2/1/46		44- 55 (glass graduate)
2/8/46	5 minutes	31- 41 (in antrum)
2/25/46	2 hours	82-131 (in antrum)
2/26/46	5 minutes	67-105 (in antrum)

These results indicate that penicillin aerosol does lodge on the mucous membrane of the antrum and may be recovered from it from five minutes to two hours after it has been introduced by catheter and syringe.

CLINICAL RESULTS

The clinical results will be presented in the accompanying tables and case reports. These cases represent all cases in which the procedure was tried, including acute and chronic cases, with and without allergic factors as well as infaction.

The clinical results of cases treated in the hospital or at home two to four times daily are summarized in Tables II and III. Dosage was 50,000 units in 1 cc. normal saline for each inhalation, unless specified differently. Of fifty-eight courses in forty-seven patients, marked improvement took place in eighteen, moderate in seventeen, slight benefit in six and no improvement in seventeen. Of thirty-one patients x-rayed before and after treatment, nineteen showed significant improvement on x-ray examination, eight no change and four showed increased involvement. In twenty-three cases in which comparative observation was present, the sputum or nasal culture showed disappearance of gram-positive organisms

such as: pneumococcus, Streptococcus hemolyticus, Streptococcus viridans, Staphylococcus aureus and Staphylococcus albus in nineteen cases. Out of twenty-seven cases in which cultures were obtained after treatment, gram-negative organisms were found in twenty-four cases.

The clinical results of clinic cases treated once daily are summarized in Tables IV and V. Of thirty-five patients, eleven showed marked improvement, thirteen moderate, eight slight and three no improvement. Out of twenty-six patients x-rayed before and after treatment, fifteen showed x-ray improvement and eleven no improvement. Inasal cultures before and after treatment in eighteen cases showed disappearance of some of the gram-positive organisms, but predominance in almost every case of some of the original gram-positive organisms, most frequently Staphylococcus aureus.

The clinical results of cases treated in office practice once or twice daily are presented in Table VI. Of twenty-nine courses in twenty-eight patients, ten showed marked improvement, thirteen moderate, three slight, and three no improvement. X-rays were taken before and after treatment in eight cases, showing some clearing in five and no change in three.

CASE I. *Chronic Sinusitis and Bronchial Asthma.* A male, thirty-three years of age, had asthma for seven years. Past history included frequent upper respiratory infections and bronchitis in childhood. Allergy history included hay fever in the late summer, and skin sensitivity to numerous allergens. For the past year he had received hyposensitizing injections for ragweed, trees, mixed grasses with little relief. Dyspnea was present on exertion. He admitted having a chronic postnasal discharge with occasional nasal stuffiness and rare headaches.

On admission to the hospital the patient was afebrile. He was moderately dyspneic and wheezed audibly. Significant findings included slight injection of the posterior pharynx with

TABLE II

CLINICAL RESULTS IN HOSPITAL PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Course	Diagnosis	Additional Penicillin Therapy	Clinical Improvement Attributable to Penicillin Therapy	No. of Daily Inhalations	Duration of Treatment (Days)	Reactions	Remarks
(1)	1	chronic	none	marked	1	10	0	Asthma improved also. Received combination of mouth and nasal penicillin inhalations
	2	chronic	aerosol	moderate	3	21	0	
	3	chronic	aerosol	moderate	3	21	0	
(2)	1	chronic	none	moderate	2	30	0	Previous antral opening
(3)	1	chronic, acute	none	moderate	4	5	0	Required ENT treatments for past few years
(4)	1	chronic	none	marked	4	21	0	Copious amounts of mucopus in trap. Acute infection 2 months after 1st course
	2	chronic, acute	none	marked	4	14	0	
(5)	1	acute	I.M.	none	5 (25,000)	13	Exacerbation of asthma	Allergic rhinitis with superimposed infection.
(6)	1	chronic	oral	marked	2-3	8	0	Had required frequent antral irrigations. Recurrence 7 months later following a common cold. Complete recovery
	2	chronic, acute	none	marked	4	10	0	
(7)	1	chronic	oral	slight	3 (100,000)	19	0	Inadequate suction due to poorly fitting nosepieces. Symptomatic moderate improvement on office therapy
	2	chronic	none	moderate	1	8	0	
(8)	1	chronic	none	none	4	3	0	Course of I.M. penicillin subsequently ineffective
(9)	1	chronic	I.M.	none	5	15	Sore, reddened tongue, aggravation of asthma, urticaria, swollen joints, fever 105°F.	Repeated antral irrigations without improvement in past. Later had bilateral Caldwell-Luc operations. Reaction slowly responded to adrenalin and ephedrine
(10)	1	chronic	none	none	4	10	Exacerbation of asthma	Radical sinus surgery and antral irrigations and polypectomy in past without relief
(11)	1	chronic	oral	none	5	9	Exacerbation of asthma	Repeated antral irrigations in past as well as submucous resection without improvement
(12)	1	chronic	I.M.	marked	4 (100,000)	7	0	After course of therapy bilateral middle turbinectomy performed with removal of some of ethmoid cells. Two months later submucous resection was performed
(13)	1	chronic	I.M.	marked	4	7	0	Sustained improvement
(14)	1	chronic	I.M.	marked	(100,000) 5	23	0	Radical sinus surgery 8 yrs. ago without improvement. Courses of I.M. and oral penicillin prior to admission without benefit. Submucous resection prior to discharge. Re-entered with only mild symptoms 10 mos. after 1st course
	2	chronic	none	marked	4	12	0	

TABLE II (Continued)

Case No.	Course	Diagnosis	Additional Penicillin Therapy	Clinical Improvement Attributable to Penicillin Therapy	No. of Daily Inhalations	Duration of Treatment (Days)	Reactions	Remarks
(15)	1	chronic	none	none	4	7	0	Previously had radical sinus surgery. Beeswax penicillin I.M. prior to aerosol. Inhalations caused dyspnea because of emphysema
(16)	1	chronic	oral	none	2	12	0	Inadequate suction due to poorly fitting nosepieces
(17)	1	chronic	I.M.	slight	4	9	0	Previous frontal surgery. Polypectomy subsequent to penicillin therapy
(18)	1	chronic	I.M.	none	4	10	Sore reddened tongue, urticaria, aggravation of asthma	Inadequate suction due to poorly fitting nosepieces
(19)	1	chronic, acute	none	moderate	4	14	0	Multiple allergies
(20)	1	chronic	none	moderate	(30,000) 1	2	0	Previously treated with penicillin aerosol by mouth inhalations for infections asthma. Radical sinus surgery, and ENT treatment in past with moderate improvement
(21)	1	chronic, acute	none	moderate	5	8	0	Asthma much improved
(22)	2	acute	none	moderate	1	3	0	Radical sinus surgery in past and repeated antral irrigations, without improvement. Residence in Arizona without benefit
	1	chronic	oral, I.M.	none	4	23	0	
(23)	1	chronic	none	none	4	8	0	Polypectomy several yrs. ago, permanent antral openings, followed by other sinus surgery, no improvement. No relief in Arizona
	2	chronic	none	none	3	14	0	
	3	chronic	none	none	4	21	0	
(24)	1	chronic	none	moderate	4	48	Exacerbation of asthma	Resumed treatment without reaction after interval on sulfacetamide aerosol
	2	chronic	none	moderate	2-3	14		
(25)	1	chronic	oral aerosol	none	2	16	Coated black tongue	Poor suction due to perforated ear drum. Treatment combined with mouth inhalation. Later had polypectomy
(26)	1	chronic, acute	none	marked	4	14	0	Antral irrigations prior to and at start of penicillin therapy. More symptomatic relief and faster x-ray clearing after aerosol with suction started
(27)	1	chronic	none	slight	3	21	0	Previously had mouth inhalations for bronchiectasis
(28)	1	chronic, acute	none	marked	2-4	15	Sore nostrils and throat	Sustained improvement for 6 months
(29)	1	chronic	I.M.	slight	(25,000) 3-4	14	0	Asthma relieved by fever therapy
(30)	1	chronic, acute	I.M. for 2 days	marked	2-4	4		Sustained improvement

TABLE II (Continued)

Case No.	Course	Diagnosis	Additional Penicillin Therapy	Clinical Improvement Attributable to Penicillin Therapy	No. of Daily Inhalations	Duration of Treatment (Days)	Reactions	Remarks
(31)	1	acute	none	slight	2-3	10	0	Allergic rhinitis with superimposed infection
(32)	1	chronic	none	none	4	14	Exacerbation of asthma	Previously had single daily treatment in clinic for 1 week without improvement. Radical sinus surgery in past with temporary improvement
(33)	1	chronic	I.M. for 2 days	moderate	4-5	10	Urticaria	Reaction occurred after penicillin changed from the calcium to crystalline potassium salt
(34)	1	chronic, acute	none	moderate	4	4	0	Allergic rhinitis
(35)	1	chronic	none	slight	4	12	0	Symptoms of sinusitis without confirmatory x-ray evidence
(36)	1	chronic	none	marked	4	21	0	Improvement in symptoms referable to bronchiectasis also
(37)	1	chronic	none	moderate	4	5	0	Previously treated at home with improvement
(38)	1	chronic	none	marked	4	25	0	Marked improvement in asthma also
(39)	1	chronic	none	none	4	14	0	Treated at home, unimproved, required surgery later
(40)	1	chronic, acute	none	marked	4	7	0	Previous I.M. penicillin and antral instillations of penicillin without benefit
(41)	1	acute	none	marked	3-4	10	0	No severe recurrences
(42)	1	chronic	none	none	4	10	0	Increased watery nasal discharge and sneezing. Polypectomy later
(43)	1	chronic	none	moderate	4	20	Sore reddened tongue	Marked improvement at first until reaction occurred. Sulfacetamide substituted. Increased wheezing later
	2	chronic	none	moderate	4	10	0	X-ray improvement subsequently when crystalline sodium penicillin used
(44)	1	chronic, acute	oral	moderate	3	12	0	Treatment followed by 15% sulfacetamide aerosol
(45)	1	chronic	none	marked	4	12	Nausea, vomiting and fever	Asthma also improved
(46)	1	chronic	none	marked	4	18	Black coated tongue	Marked improvement sustained 6 months
(47)	1	chronic	none	none	3-4	14	0	Followed tooth infection

lymphoid hyperplasia. Chest showed some increase in the anteroposterior diameter with the use of accessory muscles of respiration and poor diaphragmatic motion. Lungs were hyperresonant with scattered sibilant rhonchi in both phases of respiration.

Laboratory data were as follows: hemoglobin 14.3 Gm., red blood count 5,330,000, white blood count 7,600 with P 53 (0-12-41), L 38, E 16, M 3; ESR 73 mm. after 1 hour. Sputum culture: *Streptococcus viridans* predominating. Chest x-ray revealed increased radiolucency of

TABLE III

X-RAY CHANGES AND SPUTUM CULTURE IN HOSPITAL PATIENTS WITH SINUSITIS
TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Course	Sputum Culture		X-Ray Examination	
		Before Treatment	After Treatment	Before Treatment	After Treatment
(1)	1	0	0	Pan-sinusitis	0
(2)	1	Proteus, O. pneumoniae	0	Both antra clouded	0
(3)	1	0	0	Diffuse clouding of ethmoids	Clearing of ethmoids
(4)	1	Strep. viridans	B. aerogenes	Diffuse clouding of rt. antrum, slight clouding of lt. antrum and ethmoids, diffuse clouding of sphenoids	Modern clearing of antra and ethmoids, complete clearing of sphenoids
	2			Clouding of both antra	Clearing of antra
(5)	1	Strep. viridans	B. coli	Clear	0
(6)	1	No growth*	B. aerogenes*	Marked clouding of both antra with suggestive fluid levels, clouding of ethmoids, slight clouding of sphenoids	Marked clearing; no evidence of fluid, and only slight residual thickening of lining of antra
	2	0	0	Marked clouding of rt. antrum, mod. clouding of lt. antrum	Clearing of both antra
(7)	1	Pneumococcus, type 19	B. coli	Clouding of all sinuses with fluid levels in antra	Progressively higher fluid levels
	2	Staph. aureus, B. subtilis	0	Clouding of all sinuses	0
(8)	1	B. Friedlander	0	Clouding of left antrum and left ethmoids	0
(9)	1	Non-hemol. Strep.	B. aerogenes B. coli	Marked thickening of lining membrane of both antra, and clouding of all other sinuses	Both antra almost filled with fluid, no change in other sinuses
(10)	1	Strep. viridans	B. coli	Homogeneous dense clouding of all sinuses	No change
(11)	1	Strep. viridans Hemol. Strep.	B. aerogenes	Opaque left frontal, clouding of ft. frontal. Both antra opaque. Clouding of ethmoids and sphenoids	0
(12)	1	B. proteus	B. aerogenes	Clouding of antra, ethmoids and frontals	No change
(13)	1	Staph. aureus* B. coli	0	Clouding of antra and some ethmoid cells	0
(14)	1	Staph. albus	B. aerogenes	Marked thickening of lining membrane of both antra. Clouding of ethmoids	10 days later: Less marked thickening of lining membrane of right antrum
	2	Hemol. Staph. aureus	B. coli	No change	
(15)	1	D. pneumoniae Staph. aureus	B. aerogenes	Pan-sinusitis	No change
(16)	1	B. alkaligenes	0	Pan-sinusitis	No change except development of fluid level in lt. antrum
(17)	1	0	0	Pan-sinusitis	0
(18)	1	Strep. viridans	B. coli	Pan-sinusitis	No change
(19)	1	0	0	Pan-sinusitis	Moderate clearing
(20)	1	0	B. aerogenes	Pan-sinusitis	0
(21)	1	0	0	Moderate clouding of both antra	Clearing of antra
	2	Hemol. Strep. D. pneumoniae†	0	Clouding of antra	0
(22)	1	Hemol. B. pyocyaneus	B. aerogenes	Pan-sinusitis	0
(23)	1	0	B. aerogenes	Pan-sinusitis	No change
	2	B. aerogenes	0		
	3	0	Staph. auerus	Pan-sinusitis	0

* Nasal culture.

† Throat culture.

TABLE III (Continued)

Case No.	Course	Sputum Culture		X-Ray Examination	
		Before Treatment	After Treatment	Before Treatment	After Treatment
(24)	1	Strep. viridans	0	Pan-sinusitis	Very slight clearing
	2	Staph. aureus	0	Pan-sinusitis	Slight clearing
(25)	1	Strep. viridans	Hemol. B. coli	Pan-sinusitis	0
(26)	1	Strep. viridans*	0	Marked clouding of both antra	Clearing of antra
		Hemol. Staph. albus			
(27)	1	D. pneumoniae	D. pneumoniae	Pan-sinusitis	Pan-sinusitis less marked than prior to therapy
		Staph. aureus			
		Non-hemol. Strep.			
(28)	1	Strep. viridans	Yeasts	Marked thickening of lining membrane of both antra with clouding of ethmoids bilaterally	Complete clearing of rt. antrum and ethmoid cells with only slight clouding of inferior portion of lt. antrum
		Hemol. Strep.			
		Staph. aureus			
(29)	1	B. coli	Gram. neg. rods	Clouding of antra	0
	2	D. Pneumoniae	Non-hemol. Strep.		
		Staph. aureus			
(30)	1	No growth †	0	Clouding of ethmoids	0
(31)	1	Hemol. Strep. †	N. catarrhalis †	Slight thickening of lining membrane of both antra, right ethmoids clouded	0
(32)	1	Overgrown with proteus	B. aerogenes	Pan-sinusitis	No change
(33)	1	Slight growth †	0	Pan-sinusitis	No change
(34)	1	No growth*	0	Left frontal and right sphenoid slightly clouded	0
(35)	1	No growth*	0	Negative	0
(36)	1	Hemol. Strep.*	Negative for Hemol. Strep.	Pan-sinusitis	Increase in size of polypoid mass in lt. frontal and rt. antrum
		Hemol. Strep. †			
(37)	1	0	0	Clouding of antra	Some clearing
(38)	1	Strep. viridans	Gram. neg. bacillus	Pan-sinusitis	No change
		Staph. aureus			
(39)	1	0	0	Pan-sinusitis, opaque left antrum	0
(40)	1	Pneumococcus	0	Opaque antra; ethmoids, frontals and sphenoids slightly clouded	Progressive clearing
(41)	1	0	0	Clouding of both antra	0
(42)	1	Hemol. Strep.	0	Clouding of both antra, slight clouding of ethmoids	0
		Pneumococcus			
		Staph. aureus			
(43)	1	Staph. aureus	0	Marked thickening of lining membrane of both antra. Ethmoids slightly clouded on left	
		Non-hemol. Strep.			
		Hemol. Strep.			
	2	Gram neg. bacillus	0	Marked thickening of lining membrane of rt. antrum and clouding of left antrum	Improvement
(44)	1	Strep. viridans	B. coli	Marked clouding of rt. antrum, slight thickening of lining membrane of lt. antrum and ethmoids on right. Slight clouding of left frontal	Some clearing of rt. antrum with better aeration
	2	Staph. aureus	B. coli		
		D. pneumoniae			
		Hemol. Strep.			
(45)	1	Hemol. Strep.	0	Clouding of antra and ethmoids bilaterally	Slightly better aeration of right antrum
		Non-hemol. Strep.			
		Hemol. Staph. aureus			
(46)	1	Staph. aureus	0	Marked clouding of rt. antrum; slight clouding of lt. antrum. Right ethmoids slightly clouded	Marked improvement
		Hemol. Strep.			
		Non-hemol. Strep.			
		Staph. albus			
(47)	1	Staph. aureus	B. coli	0	0

TABLE IV

CLINICAL RESULTS IN CLINIC PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Diagnosis	Clinical Improvement Attributable to Penicillin Therapy	Total No. of Inhalations	Duration of Treatment (Days)	Remarks
1	Chronic	slight	26	44	Additional allergic factors. Improvement not sustained. Asthma also improved on therapy Allergic rhinitis underlying infection Patient returned for second course which was followed by moderate improvement Polyps and asthma. Asthma slightly improved
2	Acute	none	23	42	
3	Chronic	moderate	5	6	
4	Chronic	moderate	14	21	Marked symptomatic improvement Improvement sustained several months
5	Acute	marked	3	3	
6	Chronic	marked	9	10	
7	Chronic	marked	5	5	
8	Acute	moderate	6	7	
9	Chronic	moderate	11	15	
10	Chronic	moderate	7	8	
11	Chronic, acute	marked	7	12	
12	Chronic	moderate	8	12	
13	Chronic	moderate	20	30	
14	Acute	marked	8	8	Hospitalization necessary
15	Chronic	marked	23	31	
16	Chronic	none	6	8	
17	Chronic	slight	20	30	Slight improvement at first, later worse. Operation: antral windows Improved until sensitivity reaction Later had marked improvement in hospital on 4 daily inhalations. Asthma greatly improved. Effect not sustained over 1 month
18	Chronic	none	35	48	
19	Chronic	moderate	18	40	
20	Chronic	slight	10	14	Improvement not sustained following treatment. Asthma markedly improved. Later required antral washings Improved markedly but had penicillin sensitivity reaction Dramatic improvement
21	Chronic	moderate	65	140	
22	Chronic	marked	4	5	
23	Acute	marked	6	14	Marked improvement, but patient had antral washing
24	Chronic	slight	8	15	
25	Chronic	marked	2	2	
26	Chronic	moderate	4	7	Sensitivity reaction to both penicillin and sulfacetamide
27	Chronic	moderate	10	17	
28	Chronic	marked	8	21	
29	Chronic	slight	15	28	
30	Acute	marked	9	14	
31	Chronic	moderate	20	30	
32	Chronic	slight	4	5	
33	Chronic	slight	10	14	
34	Chronic	moderate	7	9	
35	Chronic	slight	3	4	

both lung fields. Sinus x-rays revealed clear frontals, diffuse clouding of the right antrum and probable slight thickening of the mucosal lining of the left antrum, slight clouding of the ethmoids on the right and diffuse clouding of both sphenoids. (Figs. 3 and 4.)

The patient was given a course of nasal

penicillin aerosol with negative pressure, 50,000 units (concentration of 20,000 units per cc. normal saline) four times a day for three weeks or a total of 4,000,000 units. He used 2 drops of privityne 0.1 per cent instilled into each nostril before penicillin inhalations. A large amount of mucopurulent secretion was obtained in the

TABLE V

X-RAY CHANGES AND NASAL CULTURE IN CLINIC PATIENTS WITH SINUSITIS
TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Nasal Culture		X-Ray Examination	
	Before Treatment	After Treatment	Before Treatment	After Treatment
1	Strep. viridans	Staph. aureus	Pan-sinusitis	Slight clearing
2	Staph. aureus	D. pneumoniae	Rt. frontal	No change
	Hemol. Staph. aureus		Rt. maxillary	
	D. pneumoniae		Rt. ethmoiditis	
3	D. pneumoniae	Staph. aureus	Pan-sinusitis with fluid in antra	Clearing except for right frontal
4	Staph. aureus		Maxillary sinusitis, bilateral	No change
5	Hemol. Staph. aureus		Ethmoid and maxillary sinusitis, bilateral	Clearing of ethmoids, partial clearing of antra
6	Staph. aureus		Maxillary sinusitis, bilateral	0
7	Hemol. Staph. aureus		Fluid in rt. frontal and rt. antrum	Some clearing
8	Hemol. Strep.	No growth	Maxillary sinusitis, bilateral	Slight clearing of right maxillary
9	Pneumococcus, type 7		Maxillary sinusitis, bilateral	Slight clearing on right
10	Staph. albus			
11	Non-hemol. Strep.	Staph. aureus	Maxillary sinusitis, bilateral	Clearing
	Staph. aureus		Bilateral clouding of antra, esp. rt.	Clearing
12	D. pneumoniae		Maxillary, bilateral and left sphenoid sinusitis	No change
13	Staph. aureus		Rt. maxillary sinusitis	No change
14	Staph. aureus		Lt. frontal, rt. maxillary and bilateral ethmoiditis	No change
15	Staph. aureus	No growth	Maxillary and ethmoiditis	No change
16	Strep. viridans		Anomalous development, no maxillary sinus	
17	Staph. aureus	Staph. aureus	Maxillary and ethmoid sinusitis	0
	Hemol. Staph. aureus			
	Hemol. B. coli			
18	Strep. viridans	D. pneumoniae	Pan-sinusitis	Frontals involved later
	Non-hemol. Strep.			
	Staph. aureus			
19	Negative for hemol. Strep.	Hemol. Staph. aureus	Pan-sinusitis	Clearing of right maxillary sinus
20	Hemol. Strep.			
21	Staph. aureus			
22	Staph. aureus	Staph. aureus	Ethmoiditis	No change
	Hemol. Staph. aureus			
	Hemol. Staph. aureus			
23	Staph. aureus	Non-hemol. Strep.	Bilateral ethmoid, sphenoid and maxillary sinusitis	Some clearing
24	Staph. aureus	Staph. aureus	Clouding of ethmoids and lt. antrum	0
25	Negative for Hemol. Strep.			
26	Pneumococcus, type 3			
27	Pneumococcus, type 3	Staph. aureus	Pan-sinusitis	0
28	D. pneumoniae			
	Hemol. Staph. aureus			
29	Staph. aureus	Staph. aureus	Pan-sinusitis	No change
30	Hemol. Strep.			
31	Staph. albus			
32	Non-hemol. Strep.	Staph. aureus	Left maxillary sinusitis	Slightly improved
33	Staph. aureus			
	Gram pos. bacilli			
34	Gram pos. bacilli	Gram neg. bacilli	Maxillary sinusitis, chronic, bilateral	Slightly improved
	Gram neg. diplococcus			
35	Staph. albus	Staph. aureus	Maxillary sinusitis, bilateral with fluid level on right	Right antrum completely opaque. Some clearing of left antrum
	Hemol. Strep.			
			Thickened membrane of both antra	0

TABLE VI

CLINICAL RESULTS IN OFFICE PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL
AND NEGATIVE PRESSURE

Case No.	Diagnosis	Sputum Culture Before Treatment	X-Ray Examination Before Treatment	Clinical Improvement Attributable to Penicillin Therapy	Total No. of Inhalations	Duration of Treatment (Days)	Remarks
1	Chronic, acute	Hemol. Staph. aureus† Strep. viridans Staph. aureus	Thickened membrane and fluid level in right antrum. Ethmoids and frontal clouded on left. Thickened membrane of left antrum	Moderate	3	3	X-ray clearing of left antrum. Asthma improved
2	Chronic, acute	Staph. aureus	Clouding of both antra and left ethmoids	Moderate	15	10	
3	Chronic	Staph. aureus Non-hemol. Strep.	Marked clouding of rt. antrum, mod. lt. antrum, lt. ethmoid hazy	None	22	17	Temporary improvement. Dyspneic from inhalations because of emphysema
4	Chronic	Strep. viridans	Moderate clouding of antra, ethmoids slightly clouded	Marked	10	14	Marked improvement in sense of well being, loss of fatigue and anorexia
5	Chronic	Strep. viridans H. influenzae	Clouding of both antra and ethmoids	Moderate	9	14	Numerous antral irrigations in past. X-ray after treatment unchanged
6	Chronic	Strep. viridans Hemol. strep.	Clouding of both antra and left ethmoids	None	10	14	Symptomatic improvement during treatment, not sustained. No x-ray improvement. Required submucous resection and ethmoidectomy
7	Acute	Staph. aureus D. pneumoniae	Thickened membrane of right antrum and slightly of left antrum. Ethmoids clouded	Marked	5	7	Recurrence treated with two subsequent inhalations
8	Chronic		Opaque antra and ethmoid on left	Moderate	5	5	
9	Chronic		Thickening of membrane of both antra	Slight	3	3	
10	Acute	Hemol. Strep. Pneumococcus Staph. aureus	Clouding of left ethmoid	Moderate	5	5	
11	Chronic, acute	B. coli	Both antra, left frontal hazy	Marked	2	2	Clearing of both antra by x-ray
12	Chronic	H. Staph. aureus	Clouding of both antra	Moderate	14	7	Broncho-spasm during inhalations
13	Chronic	Strep. viridans Hemol. Strep.	Thickened membrane of both antra	Marked	10	14	
14	Chronic 1st course	Hemol. Strep. Strep. viridans	Bilateral maxillary clouding, ethmoids clouded	None	10	14	Symptoms aggravated by positive pressure
	Chronic 2nd course	Strep. viridans Hemol. Strep. Staph. albus	No change	Moderate	10	14	X-ray after treatment. Slight reduction in thickening of lining membrane of both antra

* Nasal culture.

† Throat culture.

TABLE VI (Continued)

Case No.	Diagnosis	Sputum Culture Before Treatment	X-Ray Examination Before Treatment	Clinical Improvement Attributable to Penicillin Therapy	Total No. of Inhalations	Duration of Treatment (Days)	Remarks
15	Chronic, acute	Hemol. Strep. Strep. viridans Staph. aureus	Clouding of left antrum	Moderate	14	7	Sustained improvement for several months with concomitant improvement in asthma
16	Chronic	Hemol. Strep. Strep. viridans Micrococci	Clouding of both antra	Moderate	28	14	
17	Chronic		Thickened membrane of both antra, clouding of left frontal and left ethmoids	Moderate	9	14	
18	Chronic	Staph. aureus D. pneumo†	Diffuse clouding of left antrum, thickened membrane of right antrum	Slight	7	9	
19	Chronic	Strep. viridans Non-hemol. Strep.	Clouding of inferior portion of rt. antrum	Slight	10	5	Clinical recovery. Asthma relieved Clinical recovery
20	Acute	0	Clouding of both antra and ethmoids	Marked	4	6	
21	Chronic, acute	Staph. albus* Staph. aureus* Strep. viridans Hemol. Staph. aureus	Thickened membrane of both antra	Marked	10	12	
22	Chronic		Markedly thickened membrane of lt. antrum, and slightly of rt. antrum. Some clouding of rt. ethmoids and left frontal	Marked	14	14	X-ray after treatment: Some improvement
23	Chronic		Homogeneous clouding of both antra, frontals and ethmoids	Marked	5	14	
24	Chronic, acute	Non-hemol. Strep. Staph. aureus D. pneumococcus	Thickened membrane of both antra, ethmoids clouded	Moderate	60	21	Symptoms aggravated following submucous resection two years ago Culture unchanged. Marked improvement in first 2 wks., when developed an acute infection which responded less well to treatment
25	Chronic, acute	Hemol. Strep. Staph. aureus D. pneumoniae	Clouding of both antra and left ethmoids	Moderate	10	14	
26	Chronic	No growth	Clouding of rt. antrum, thickening of lining membrane of left antrum, ethmoids clouded	Marked	23	15	X-ray after treatment unchanged. Previously had no symptomatic improvement with nasal penicillin by atomizer spray Culture after treatment: Gram neg. rod. X-ray after treatment: some clearing
27	Chronic, acute	0	Slight clouding of antra and ethmoids	Moderate	28	20	
28	Chronic, acute		Marked clouding of right antrum	Marked	10	5	Had nausea, chilliness and fever after 1st few inhalations, later no reaction

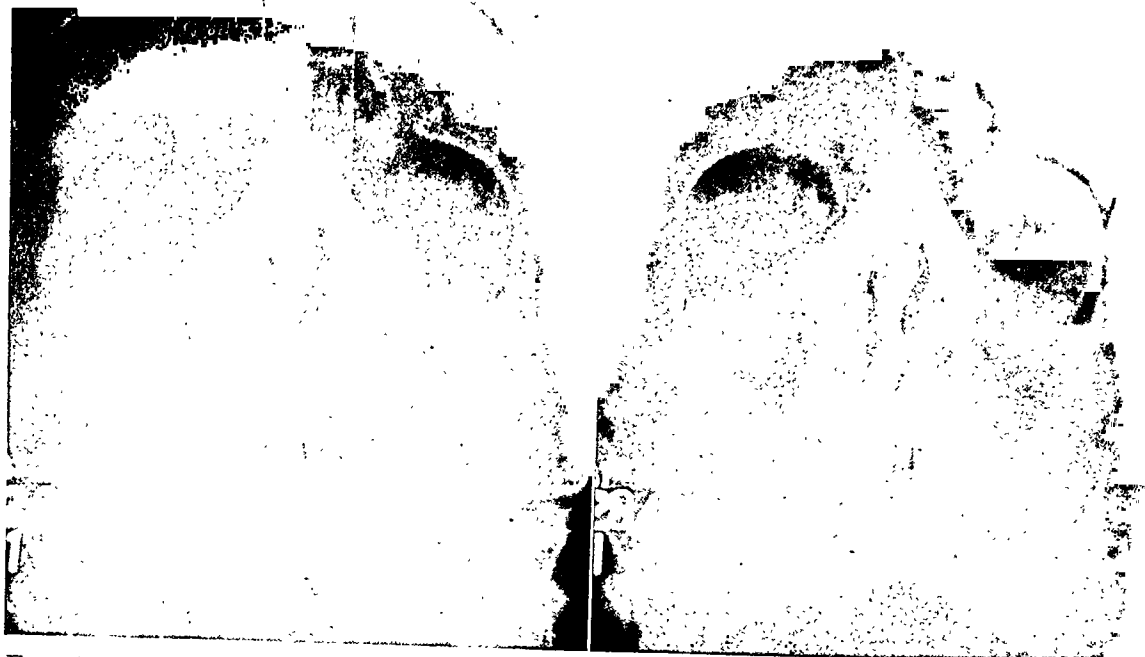


FIG. 3. *X-rays of sinuses before treatment (left) and eight days after start of treatment (right), revealing marked clearing of right antrum and slight clearing of left antrum.*

trap of the apparatus. The only other medication consisted of oral aminophyllin, ephedrine, potassium iodide and nebulized Vaponefrin.

There was marked relief of symptoms of asthma and sinusitis. Nasal passages became clear and there was little post-nasal drip. The course was afebrile. Cough and expectoration decreased about 75 per cent. Dyspnea was not observed except on undue exertion. Mild wheezing occurred infrequently. Sputum culture showed *Bacillus aerogenes* predominating. ESR fell to 17 mm. after one hour. Lungs were clear on physical examination, although breath sounds were distant. Sinus x-rays eight days after starting penicillin nasal suction treatment revealed considerable clearing of the clouding previously noted in the right antrum, right ethmoids and complete clearing of the sphenoids.

Following discharge, the patient remained well for two and one-half months with occasional use of Vaponefrin spray and oral aminophyllin. At that time he developed an acute sinusitis with frontal headache, nasal obstruction and mucopurulent discharge. There was some exacerbation of his asthma. The sinus x-rays revealed clouding of both antra although the sphenoids remained clear. (Fig. 5.) He was treated at home with a course of nasal penicillin

aerosol with negative pressure, 50,000 units in 1 cc. normal saline four times a day for a total of ten days or 2,000,000 units. At that time his symptoms had entirely disappeared and his sinus x-rays showed clearing. The patient has remained well during the three months since the second course of treatment and has been doing eight hours of sedentary work daily.

CASE II. Chronic Sinusitis. A white, married woman, forty years of age had a history of sinusitis ten years ago. Since that time she had no acute symptoms until one week before office consultation when following a cold she complained of nasal discharge and obstruction, intermittent headache and slight fever to 99.4°F. She was put at rest in bed, penicillin was administered 20,000 units intramuscularly every three hours, and penicillin aerosol 50,000 units per cc. was inhaled every three hours during the day *without* negative pressure. In addition, penicillin was instilled by a nose and throat consultant three times during this period of seven days' treatment.

At the end of one week of combined therapy the patient's symptoms persisted; x-ray of the sinuses revealed diffuse clouding of the antra as seen in the accompanying photograph. (Fig. 6.) Penicillin by intramuscular injection

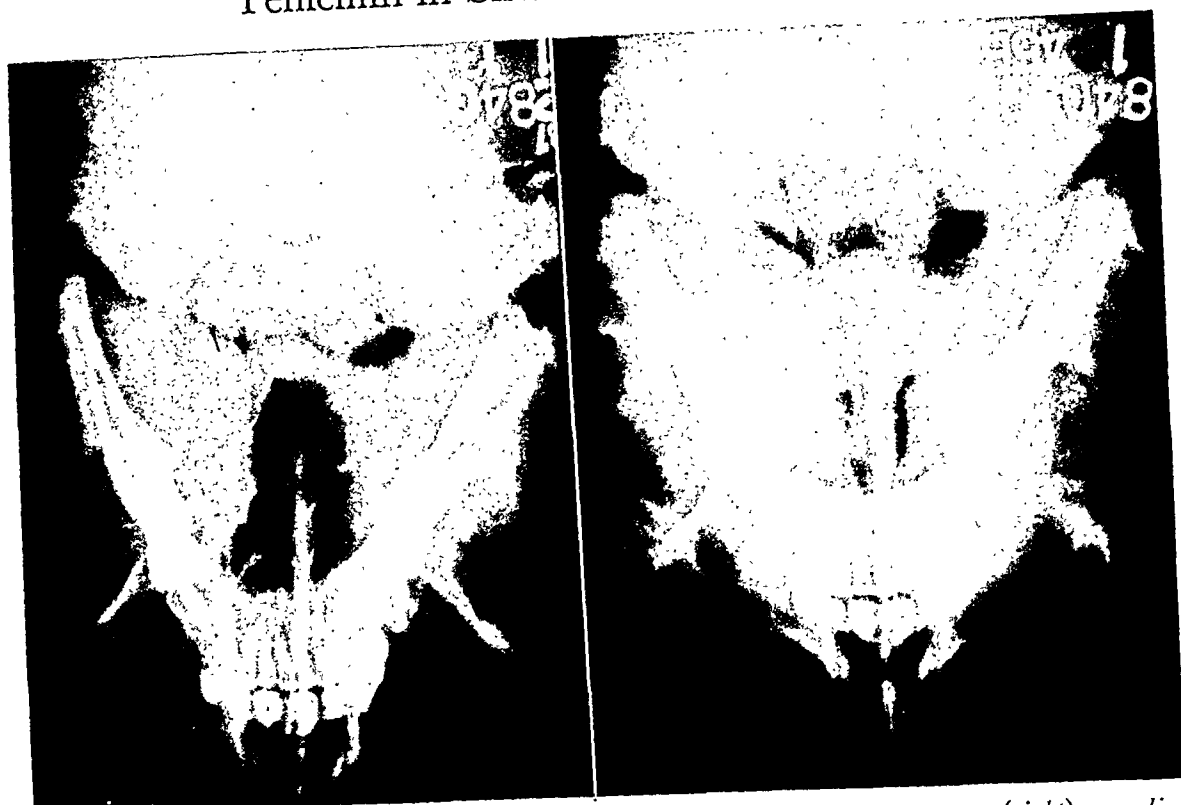


FIG. 4. X-rays of sinuses before treatment (left) and eight days after start of treatment (right), revealing complete clearing of the sphenoids.



FIG. 5. Sinus x-rays before second course of treatment (left) and after treatment (right) showing moderate clearing of both antra.

was then stopped as well as instillations into the antra. The patient was then given four inhalations of 50,000 units of penicillin per cc. normal saline with negative pressure, the oxygen flow being maintained at 6 liters per minute. Improvement began in two days and was progressive from then on, no symptoms being

present at the end of seven days; treatment was stopped and the subsequent x-ray showed improvement. An x-ray one month afterwards revealed further clearing of the process in both sinuses except for what was interpreted as a polypoid formation in the mucous membrane in the lower part of both antra.



FIG. 6. Sinus x-rays after one week of control therapy (left), after one week of penicillin aerosol with negative pressure (center) and one month later (right) showing progressive clearing.

The patient was well for eight months when an acute sinusitis took place swiftly after a head cold. X-ray of the sinuses showed a slight diffuse clouding of both antra. She was treated with inhalation of 50,000 units of penicillin per cc. normal saline with negative pressure, once a day for two days when symptoms cleared and the patient refused further therapy or x-ray examination. She has been clinically well for the seven months since then.

Comment. In this patient a control period of intramuscular injection and nasal inhalation of penicillin, combined with instillation of penicillin in solution, 500 units per cc. into the antra, was carried out without clinical benefit. The subsequent treatment with penicillin aerosol and negative pressure brought prompt relief with symptomatic complete recovery.

CASE III. *Chronic and Acute Sinusitis.* A female, thirty-three years old, gave a history of recurrent sinusitis of ten years' duration. During the previous two weeks she complained of increasing headache, obstruction and discharge. X-ray showed bilateral involvement, especially the right antrum. Ear, nose and throat examination revealed bilateral overflow of mucopurulent secretion. She was treated in the clinic receiving seven treatments in twelve days, one treatment per day, 40,000 units per cc. normal

saline. X-ray and ENT examination showed clearing of the infection. (Fig. 7.)

CASE IV. *Chronic Sinusitis and Pulmonary Emphysema.* A male, fifty years of age was admitted to the hospital for oxygen therapy because of pulmonary emphysema. He had a history of sinusitis for many years with symptoms of headache, nasal obstruction, post-nasal discharge. History includes arrested tuberculosis of the left upper lobe.

The patient was a well developed, well nourished middle-aged man moderately dyspneic in the oxygen chamber (concentration 50 per cent). No cyanosis was present. The pharynx was moderately reddened. The chest was barrel-shaped and the patient used the accessory muscles of respiration. Lungs were resonant except for slight dullness at the left posterior top. Expiratory note was prolonged and breath sounds were diminished and distant throughout both lungs. A few subcrepitant râles, increased after cough, were audible on the left posteriorly above D 5.

Laboratory data were as follows: hemoglobin 17.7 Gm., red blood count 6,280,000, white blood count 9,550 with P 52 (0-2-50), L 31, M 15, B 2; ESR 25 mm. after one hour; serum CO₂ 62.6 volumes per cent. Sputum culture revealed *Staphylococcus aureus* and non-hemolytic streptococcus. X-ray of the chest revealed mottled fibrotic infiltration in the upper one-third of the left lung field; emphysematous appearance of remainder of the lung fields with

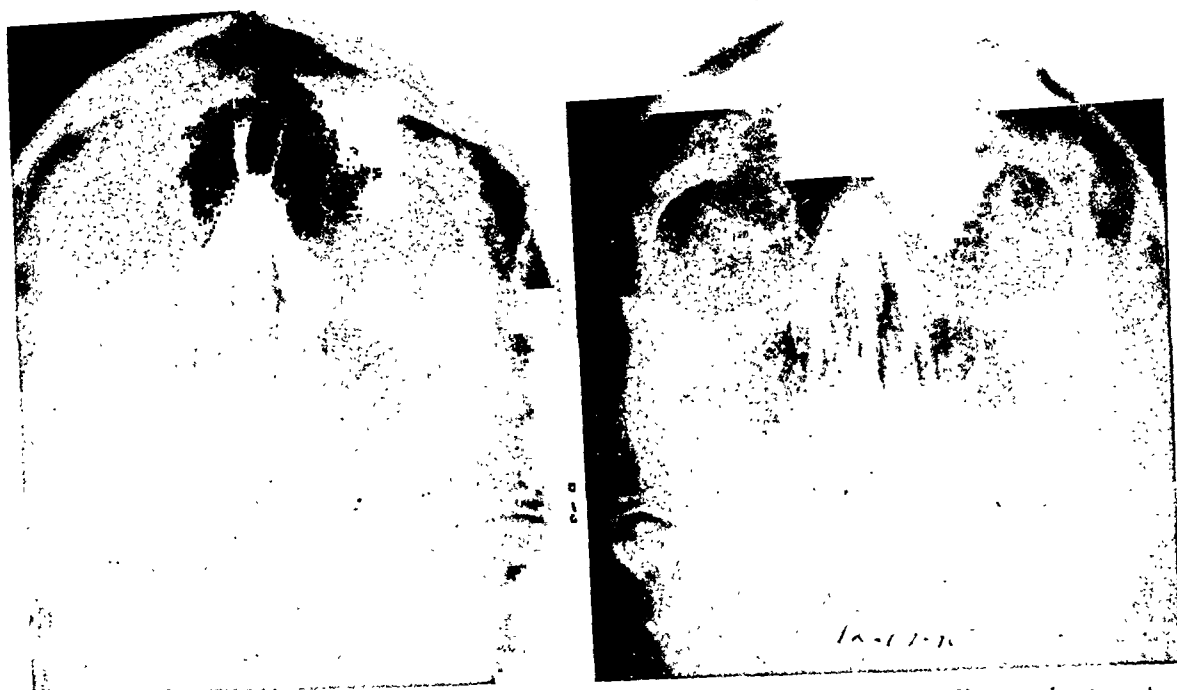


FIG. 7. X-rays of sinuses before treatment (left) and after treatment (right), revealing moderate antral clearing with some residual thickening of the lining membrane.

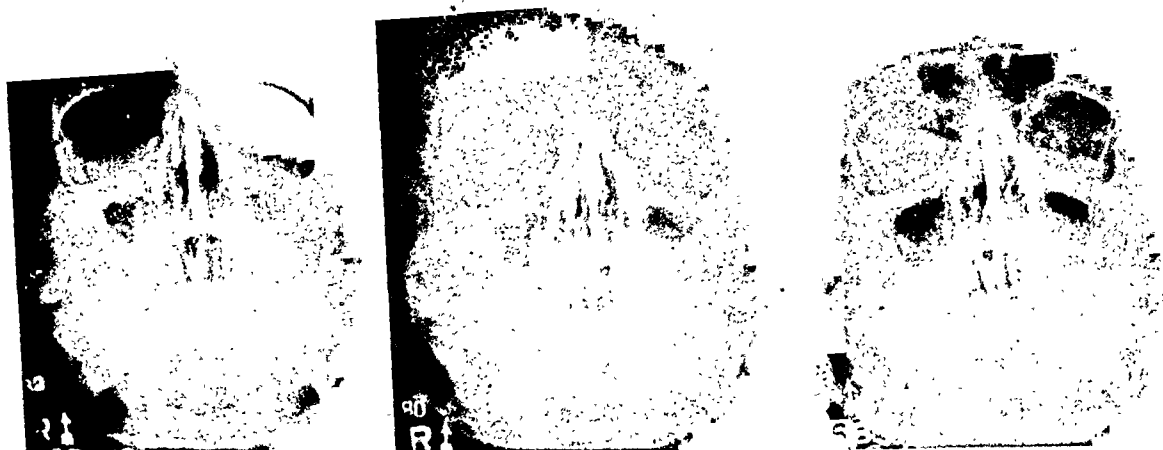


FIG. 8. Sinus x-rays before treatment (left), during treatment (center), and after treatment (right) showing increased involvement of left antrum eight days after start of therapy but final complete clearing of right antrum with moderate clearing of left antrum.

bullae. Sinus x-ray showed considerable thickening of the lining membrane of both antra with clouding of the ethmoid cells on the right and a lesser clouding on the left. (Fig. 8.)

Combined penicillin oral inhalations and nasal inhalations with negative pressure were given for a nine-day period, the patient receiving a total of 400,000 units (40,000 units once or twice daily), by oral and 600,000 units (25,000 units two to three times daily) by nasal inhalation. At this time the sinus films showed no change in the right antrum or ethmoids, but a

further increase in density with suggestion of fluid in the left antrum, although the air-containing portion appeared clearer. Sputum culture showed *Streptococcus viridans*. Serum CO_2 rose to 69.2 volumes per cent. The patient was discharged to continue nasal inhalations at home since his pulmonary status was markedly improved. He was afebrile throughout his hospital stay.

He was re-admitted four days later because of acute overdilatation of the lungs, apparently precipitated by undue exertion. Nasal penicillin

aerosol was stopped two days later because of soreness and redness of the nostrils and sore, reddened throat, as well as evidence of bronchospasm. Sinus x-rays, however, showed complete clearing of the right antrum and ethmoid cells, with only slight clouding of the inferior portion of the left antrum persisting. (Fig. 8.) Bronchopulmonary symptoms responded in several days to therapy with continuous oxygen, demerol, aminophyllin, ephedrine and Vaponefrin-neosynephrine spray. The patient was discharged in two weeks markedly improved. Sinus x-rays two months later showed maintenance of improvement.

A patient was seen recently in whom symptoms of sinusitis of four weeks' duration were present combined with cough and expectoration of considerable quantities of mucopurulent material. A hemolytic staphylococcus aureus was isolated from the sputum and from a nasal culture. She was treated with one inhalation a day of penicillin aerosol, containing 50,000 units per cc., with negative pressure for four days. At the same time aminophyllin 0.2 Gm. was prescribed on arising and at 3 P.M. demerol was administered by mouth, 50 mg. after lunch and on retiring. Within a period of five days the cough, expectoration, nasal discharge and obstruction had almost entirely disappeared. No further follow-up was possible since she decided that she was clinically well, although x-ray had previously shown marked clouding of both antra.

COMMENTS

The results presented above indicate that acute and chronic sinusitis may in some cases be effectively treated by nasal inhalation of penicillin aerosol in conjunction with negative pressure in the nasal passages and sinuses.

Difficulties are inevitably encountered in appraising the value of any new therapeutic procedure. In the treatment of sinusitis primary consideration must be given not only

to the infectious agent, but to the presence of allergic factors. In patients with acute sinusitis *without* hypersensitivity to dust and other inhalants therapeutic benefit may be achieved in a variety of ways. Rest in bed, application of vasoconstricting solutions or inhalations of steam are followed in some cases by recovery. In other cases, washing out the antra through the natural orifice results in adequate drainage and prompt recovery. The intention of this presentation is not to suggest that penicillin aerosol with negative pressure is necessarily better than other forms of treatment, but that it is an additional procedure that may be used in infectious sinusitis and that it has been found to be of therapeutic value in acute, subacute and chronic cases.

Patients with chronic sinusitis frequently reveal both an allergic and infectious etiology. Patients in this category who have been treated once a day in the clinic have frequently shown little or no benefit. Others who have been treated three to four times a day have shown moderate improvement but with a tendency to relapse. In cases sensitive to cat hair or other substances allergic swelling of the nose may interfere with antral drainage and predispose to subsequent infection. However, patients with chronic purulent sinusitis who have been previously treated by antral irrigations with only temporary benefit and with persisting symptoms and pathological conditions in the sinuses have in some instances obtained marked and prolonged benefit. These patients are not considered permanently cured as reinfection may take place.

In cases of sinusitis with associated bronchitis aminophyllin is generally of significant therapeutic value in relieving cough, even without overt signs of bronchospasm such as sibilant râles. Demerol is generally more effective than codiene, and the combination of demerol and aminophyllin is frequently of dramatic value in the treat-

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ment of acute and subacute as well as chronic bronchitis. When demerol is administered by mouth it is important that the patient rest for two hours after ingestion in order to avoid symptoms of dizziness.

The complication of urticaria may take place but this is infrequent and may now be effectively handled by administration of benadryl. Patients with an allergic history are more apt to develop urticaria than those with a purely infectious basis.

In our experience calcium penicillin has been better tolerated than the sodium salt, and at present crystalline penicillin seems preferable to either.

Although a blood level of 0.1 to 0.2 units per cc. of serum is generally obtained with oral inhalation of penicillin aerosol, the use of this dosage with the negative pressure rebreathing device does not result in sufficient absorption through the lungs to provide any more than a minimal (0.025 to 0.05 U/cc. serum) or no detectable blood level. We have previously shown that the amount of penicillin in the blood is substantially less when inhalation of penicillin takes place through the nose instead of the mouth.

Since negative pressures of 50 to 60 mm. Hg are intermittently produced in the antrum by the technic employed, it is evident that aeration of the sinuses takes place with replacement of penicillin mist for the air previously present in the antral cavity. To what extent therapeutic results may be obtained by intermittent negative pressure itself has not been determined but it seems a sounder practice to facilitate the deposition locally of penicillin particles. Studies are in progress in which other chemotherapeutic aerosols are used, such as 5 per cent sulfathiazole, 15 per cent sulfacetimide, 0.25 per cent p-chlorophenol and streptomycin. Evidence has been presented that the therapeutic agent does actually lodge in infected mucous sinus membrane since antral wash-

ings have contained penicillin after this type of treatment. Since there is no way of determining how much penicillin is absorbed from the membrane before the washings, or how much clings to the mucous membrane after the washing, the concentration of penicillin in the antrum cannot be determined.

SUMMARY

Nasal inhalation of penicillin aerosol in conjunction with negative pressure in the nasal passages has been described as a treatment for acute and chronic sinusitis. An apparatus which also produces a slight positive pressure in addition to negative pressure during inhalation of penicillin nebulin is reported.

A negative pressure in the antra of 50 to 60 mm. Hg has been demonstrated with the procedure used. Washings from the antrum in selected cases revealed that penicillin was introduced following inhalation of 50,000 units of penicillin aerosol in conjunction with repeated negative pressure.

Cases of acute paranasal sinusitis are reported in which clinical recovery took place with one to four treatments per day over a period of three days to two weeks. Patients with chronic sinusitis are described in which marked improvement was demonstrated by x-ray and clinically with four treatments daily over a period of twelve days or more. Cases with chronic paranasal sinusitis treated once a day have frequently shown little or no significant benefit. In those patients in whom allergy is a prominent etiological factor less favorable results may be expected. Clinical improvement has been obtained in cases in which both infectious and allergic causal factors were definitely present.

Inspection of the tables and case reports illustrates the effect on the course of the disease in individual patients; a summary of the clinical results may be stated as

follows, using the combined findings of hospital, home, clinic and office patients: Of 122 courses of therapy in 110 patients, marked improvement took place in thirty-nine, moderate in forty-three, slight in seventeen and no improvement in twenty-three.

Of sixty-five patients x-rayed before and after treatment, marked or significant improvement was observed in thirty-nine, no improvement in twenty-two and progressive involvement in four.

In forty-one patients in whom comparative cultures of the nasal or sputum cultures were available, disappearance of gram-positive organisms found prior to treatment took place in twenty-four. In twenty-five of these cases gram-positive organisms were found after treatment, either as the predominating organisms or in significant numbers.

The method of treating sinusitis by penicillin aerosol and negative pressure appears to be a practical procedure that produces little or no discomfort.

This report is intended as an exploratory study on the principles, methods and early clinical results of its use rather than as any final appraisal of its value.*

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Conference on Therapy

Treatment of Coronary Artery Disease*

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. The next report will appear in the November issue and will concern a continuation of the same topic.

DR. HARRY GOLD. There are several clinical varieties of coronary artery disease. Pain in the precordial or substernal region, or other areas of the chest, presents one of the chief problems. The pain is linked to a variety of factors. There is the pain associated with emotion or physical exertion, particularly walking, as occurs in the more usual type of angina of effort. There are those in whom attacks of pain frequently occur while the patients are at rest and awaken them at night, the pain of angina decubitus. There is the attack of acute coronary thrombosis or myocardial infarction. Pain, however, is not the sole problem in the management of coronary artery disease. Although there is a good deal of overlapping in the therapeutic problems presented by the clinical varieties of coronary artery disease, several of them present problems peculiar to themselves and require special attention. The list of drugs is a fairly large one; it includes morphine, demerol, codeine, barbiturates, nitrites, aminophylline, papaverine, quinidine, digitalis, mercurial diuretics and others. Views concerning the methods of their use and their value are not entirely in accord. How the evidence stands may emerge from the discussion in the conference today. Dr. Eggleston will make the opening remarks.

DR. CARY EGGLESTON: Dr. Gold left out

one form of coronary artery disease the treatment of which might be discussed, namely, that form which is discovered in the asymptomatic stage. Coronary artery disease is probably the most prevalent of all forms of heart disease and certainly is the most prevalent past the age of fifty. It may exist for a long time before any particular symptoms direct the patient's attention to the disease. From the point of view of therapy, however, we can confine our discussion largely to the types that Dr. Gold has just mentioned.

The anginal syndrome, or angina pectoris, or pain in the chest secondary to coronary artery disease, occurs most commonly as the result of effort. On the basis of rather critical and extensive analysis it is believed to be due primarily, or chiefly, to a relative myocardial anoxemia, that is, a reduction in the amount of oxygen carried to the heart muscle in relation to the amount of work that the muscle is being called upon to do. Consequently, it is commonly associated with effort or other factors which increase heart work. We cannot afford to overlook the fact that emotional stresses and strains, that a distended abdomen from any cause whatsoever, that reduction in the oxygen carrying power of the blood by anemias, and the like, are all mechanisms working in the same direction and all may

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be productive of angina pectoris or the anginal syndrome in the susceptible individual. In addition to this, the state of the nervous system is of great importance to the patient who is a victim of angina. That this plays a rôle is indicated by the relative rarity of angina in phlegmatic individuals, and by its increased incidence in patients who are of a high-strung, emotional, nervous temperament. This, undoubtedly, is a factor of some importance in the frequency of recurrence of anginal seizures. Patients who are overweight not infrequently are subject to angina, but the syndrome by no means spares the underweight or lean. Changes in temperature, sudden cold, chilling, wind and particularly cold wind, precipitate anginal seizures. Other more or less trivial factors of causation may be passed over so that we may approach immediately the question of management.

Before drug therapy is considered one should have made a critical analysis of the factors which induce anginal seizures in the individual patient and then set about by a process of education and analysis of the situation pertaining to that individual patient, to eliminate as many of those precipitating factors as possible. After this has been accomplished—and its accomplishment depends, in large measure, on the cooperation of the individual, and that, in turn, is related to his intelligence and his ability to understand the mechanisms involved in the production of his seizures—then one can pass to the consideration of medicinal or drug therapy.

One of the oldest and most commonly used remedies is alcohol. A small drink of a reasonably strong alcoholic beverage, such as brandy or whisky, by peripheral vasodilatation, we believe, will often relieve the seizure of angina pectoris. Warming of the body relieves angina pectoris. When the patient comes to rest, ceases his exertion,

angina pectoris passes rapidly. The dangers of alcohol are the dangers of inducing, possibly, some dependence on the drug, or addiction.

There are other agents which do not give rise to this difficulty. Paramount in importance are the nitrites. Many nitrites are available; some act rapidly, others slowly. One of the earliest used was amyl nitrite, rather an evil smelling, very volatile liquid which is difficult to employ because of its high volatility and must be used in the form of pearls, little glass capsules which are broken by the patient at the time of his seizure. It produces disagreeable secondary symptoms which the patient must endure if he is to use it. They consist of a general sense of discomfort, a wave of warmth over the blush area, a feeling of fullness or of bursting and throbbing in the head, particularly in the temporal region and in the neck. However, amyl nitrite acts within a few moments in the majority of instances, and synchronous with the flushing, sometimes even preceding it, there is a beginning relief of the seizure of pain. Another objection to amyl nitrite is that the pearls frequently break by exposure to ordinary changes in temperature. I have known more than one instance in which a box of amyl nitrite pearls exploded spontaneously after being carried around in a physician's bag for a short period of time. More satisfactory than amyl nitrite is nitroglycerin which is available most conveniently in the form of hypodermic tablets. These should be reasonably fresh because they tend to lose potency either from deterioration or evaporation. The smallest dose which is effective is the dose which should be employed. Many physicians have fallen into the practice of using routinely a dose of $\frac{1}{100}$ gr. or 0.6 mg. This is usually larger than is needed by the patient, and is accompanied by disagreeable side effects, which are closely similar to those that I have just

recounted for amyl nitrite. One can sometimes relieve the attack equally well with one-half of that dose, 0.3 mg., or $\frac{1}{200}$ gr., sometimes even with a smaller amount. It is wise to test out the patient's responsiveness and let him use the smallest dose which will give relief. The drug is rapidly absorbed from the buccal mucosa. The tablet should be put into the mouth, chewed but not swallowed. Effects will develop within a few minutes. Relief, if it is obtained, follows promptly and the dosage may be repeated as frequently as necessary. Although relief may be readily obtained in this way, the goal of the physician should be to guide the patient away from unnecessary medication by the previous plan of education. Other nitrites are less serviceable, in my experience, than nitroglycerin. Erythrol tetranitrate, octyl nitrite, sodium nitrite and many others are possessed of reasonably rapid action but slower than nitroglycerin.

If the attack does not pass off within a few minutes after one or two doses of nitrites, doubt concerning the diagnosis of angina should be entertained. They are, therefore, of some, although very limited, diagnostic value.

Nitroglycerin may also be used as a preventive of angina in small doses, $\frac{1}{200}$ gr. or 0.3 mg. or thereabouts, taken prior to exposure to factors which previously have precipitated attacks. Knowledge of this action may permit patients to undertake, in emergency, tasks which otherwise would be interrupted by intolerable pain.

I do not know of any other agents that are really effective in the treatment of the seizure of angina pectoris, or that compare favorably with the two that I have mentioned, namely, alcohol and nitroglycerin. We have tried the administration of aminophylline, a dose taken three or four times a day, on the theory of its dilating the coronary arteries. In some patients it seems to diminish the frequency of the attacks. It,

however, is by no means trustworthy for this purpose. It has a tendency to make the patient a little bit more alert than usual. It often makes him nervous and should be combined, therefore, in such patients with the administration of a mild sedative, such as phenobarbital in a small dose.

The second type of symptomatology from coronary artery disease is that of myocardial infarction, so frequently miscalled coronary occlusion. Myocardial infarction may occur without coronary occlusion and it is the infarction of the myocardium that is important rather than the occlusion of the coronary artery. The symptoms differ from those of angina pectoris in a few dramatic respects that are easily recognizable and make the diagnosis comparatively simple. In the first place, it is usually spontaneous in its origin. The pain appears without relation to effort or emotional stress or strain, or perhaps I would be more accurate if I said, without necessary relation. It is located in the same areas. It has the same general characteristics, but it does not respond to rest, to alcohol or to nitroglycerin. A precordial pain, or pain in the shoulders or neck, which comes on abruptly and does not respond to these measures, should be thought of as a possible myocardial infarction. If the infarction be minor, there may be few or no other immediate symptoms. The pain and associated symptoms may last for many minutes to several hours if untreated.

With an infarction of the myocardium we are faced with a train of potentialities that may be serious or even fatal. Sudden death may occur while the patient is sitting quietly in his chair or during any degree of activity. There is nothing we can do for this because we do not reach the scene in time, and it is questionable, even if we did, whether treatment would be effective. In the majority of cases the patient makes a partial recovery spontaneously after a brief

period of time, measured usually in hours, sometimes in days. During this early period the patient may show any one of a train of symptoms which demands some medical care. He may go into an early collapse or shock. He may merely complain of nausea and vomiting and break out in a profuse cold sweat. He may have disturbances of his bowel function and of the bladder.

Once the diagnosis is suspected, therapeutic steps should be taken. The patient should be put at complete rest. By "complete rest," we mean no voluntary activities on the part of the patient. This should not be continued for too long a time lest we induce thrombosis in the veins of the lower extremities and complicate the picture. But that does not occur promptly. The most immediate measure is the administration of one of the opiates. Any opiate that is available may be used. I prefer morphine, dilaudid or pantopon, but whatever opiate is present and available should be administered. The dose should be enough to relieve the patient of symptoms. In the case of morphine this is seldom less than 15 mg. and may be two or three times that dose. Corresponding doses are higher in the case of pantopon, lower in the case of dilaudid.

One may then consider the use of other sedatives, or one may turn to the use of oxygen because the embarrassment of the cardiac circulation is very great and these patients often present a picture of relative anoxemia. Oxygen by inhalation often relieves the pain and it diminishes the amount of opiate that is necessary. This should be continued as long as may be needed. The opiates should be replaced, I believe, as soon as possible by other sedatives. The barbiturates are the sedatives of choice. Hydrated chloral may be used, but the barbiturates are usually well borne and are usually quite effective, the idea being to keep the patient at mental and

emotional rest during the earlier stages of his convalescence from the acute attack.

If the attack be more severe, the patient may develop symptoms suggestive of pulmonary edema or may actually go into pulmonary edema. This probably is best met, in addition to the use of opiates and oxygen, by the intravenous injection of aminophylline, 0.24 to 0.48 Gm., given slowly, intravenously. By "slowly" I mean within a period of five to ten minutes. This will often relieve the symptoms of pulmonary edema. Atropine in large doses may relieve it, in doses of 2 mg. or thereabouts. If it be very urgent, this may be administered intravenously, or preferably intramuscularly or subcutaneously.

Papaverine has been advocated by a good many. By mouth, in my experience, it has been useless. It must be injected subcutaneously or intravenously to be of any value. Its purpose is relaxation of the vessels. I do not consider it a highly trustworthy or valuable agent in these conditions.

Atropine has recently been hailed as highly effective in coronary thrombosis, aside from its use against pulmonary edema. My own experience with it has been rather unsatisfactory.

Then, there is another picture of myocardial infarction, that in which the patient presents, in addition to those just recounted, symptoms of acute and progressive congestive heart failure. Under these circumstances one must resort to digitalization. I do not think I need to say much about digitalis or its administration if Dr. Gold or others here have talked to you about it. For immediate digitalization we may use either digitoxin, that is digitaline native, or purosigin, or the digitoxin that is now on the market by Squibb, or we may use ouabain, or digitalis leaf, or a liquid preparation of digitalis as conditions demand. For rapid use, however, one of the preparations to be introduced intravenously

is preferable, although under these circumstances I think we must remain a bit cautious in the rapidity with which we digitalize the patient. In a heart that has suffered a more or less extensive and an undetermined degree of myocardial destruction, we may do harm by too rapid digitalization. Probably the wisest procedure, therefore, would be to give digitoxin by mouth, giving a full digitalizing dose of 1.2 mg. according to Dr. Gold, or 1.5 mg. according to my experience. The difference is a minor matter. Give it by mouth and then follow up with a maintenance dose. If we use ouabain, not over 0.5 mg. should be injected initially, and none if the patient has been taking digitalis. But I am assuming that the patient has not. Then the remainder of a dose of 1 mg. total for the first twenty-four hours may be administered in fractions of your own choice, anywhere from 0.1 to 0.2 or 0.3 mg. per fraction.

Measures to combat loss of water and of salt, such as clysis or slow infusions of glucose in water or glucose in physiological saline should be used. Morphine is continued until the patient begins to recover.

DR. GOLD: Dr. Pardee, have you any special points you would like to make before this subject is opened for general discussion?

DR. HAROLD E. B. PARDEE: I would stress one character of the symptomatology which I do not think has been sufficiently emphasized, namely, symptoms of shock. Some of these patients are evidently in shock, almost pulseless, with marked fall of blood pressure, and with other signs associated with shock. In these cases, I think we have to consider one other feature of therapy, and that is, how much we shall attempt to increase the blood volume. The use of intravenous glucose should be considered, either as injection of 50 per cent glucose or as a slow intravenous drip. There is the danger in these cases that, if

one gives too much liquid, one may induce cardiac failure. There may be some protection in the falling blood pressure; it can, however, go too far.

DR. GOLD: Dr. Stewart, have you anything to add?

DR. HAROLD J. STEWART: I have very rarely seen a patient who went into shock who did not do very well. As a matter of fact, there have been some observations, which I think were reported to the Society for Experimental Biology and Medicine, in which the patients were put under luminal right after they had coronary occlusion, to the point where they were almost in a state of shock. The patients that I have seen treated for shock *per se* have usually done very badly. If the patients receive extra fluid intravenously or if glucose is given intravenously, fluid is drawn into the blood stream and the extra blood volume may do more harm than good.

So much for that side of it. On the other hand, I very rarely use luminal in a patient who has had acute coronary occlusion because of the lowering of blood pressure which may occur with this drug; consequently, that one sign which you may have to use as evidence of a coronary occlusion, namely, fall in blood pressure, cannot be relied on and you may obscure the diagnosis.

DR. EGGLESTON: May I ask if that type of patient usually requires a sedative in your experience?

DR. STEWART: In the early stages I would prefer the use of morphine or codeine to luminal as a usual procedure.

DR. WALTER MODELL: I would want to know why patients in shock with coronary disease are not given plasma. Perhaps, the reason they do not do so well is that they do not receive plasma but glucose in saline instead.

DR. STEWART: I would not give them plasma for the same reason I would not give them glucose intravenously.

DR. GOLD: Would you give them plasma, Dr. Pardee?

DR. PARDEE: I have not, as a matter of fact, used it but I think it would be good.

DR. GOLD: Would you give it, Dr. Eggleston?

DR. EGGLESTON: I would.

DR. GOLD: How much would you give?

DR. EGGLESTON: Depending upon the patient's response. I doubt if I would go above 300 cc. maximum and probably stay well below that, about 200 cc. I have not had much experience with it because it has not been very readily available and I have had to resort to other measures, chiefly glucose or clysis of glucose. I should have mentioned this. We have to restore the fluid and clysis is safer than intravenous infusion.

DR. GOLD: Dr. Stewart, what would you do in the case of a patient who has had an attack of coronary thrombosis and you see him about four hours later; he has a blood pressure of about 60 and a heart rate of 120; he has extreme thirst; the respiration is depressed and he is cold and clammy?

DR. STEWART: Put him in an oxygen tent and let it go at that so far as treating shock is concerned, I think.

DR. GOLD: It is my experience that patients who have had a coronary thrombosis and are in advanced shock, are apt to do badly, and a high proportion of them fail to survive no matter what treatment they receive. I firmly believe, however, that some of them, who would otherwise succumb, can be saved by the use of plasma. The discussion here reveals the state of general experience with plasma in the shock of coronary thrombosis. Its use in these cases is certainly not very general. I have used it many times; and it is hard to escape the conviction that in occasional cases of severe collapse following a coronary thrombosis, it has supplied the necessary boost to insure recovery. I refer, of course, to cases in which the skin is cold and clammy, the pulse is rapid, the blood pres-

sure is either so low or the pulse so feeble that the pressure cannot be registered with the usual method, or registers by an occasional sound at a level of 60 or 70 mm. mercury. I rarely advise it in the milder cases of circulatory depression following a coronary occlusion in which the blood pressure may decline to a level of around 100 mm. systolic. Most of these patients seem to have a fairly satisfactory circulation. Their skin is warm and the heart beat may be fairly slow. In the vast majority of such cases, the circulation rights itself and plasma may be withheld because, while it may be advantageous, it is not free of dangers. It is easy to overload the heart during the infusion of plasma, in which case the patient is seen to develop respiratory distress and pulmonary râles while plasma is entering the circulation. Judgment is necessary in regard to the dose of plasma. I follow the practice of injecting about 250 cc. in the first hour. If the blood pressure is boosted to levels close to 90 or 100 mm. mercury, the injection is interrupted and the blood pressure taken at frequent intervals. If the pressure resumes its downward course, more plasma is injected, and it is continued in the endeavor to maintain the pressure at a level of at least 90 or 100 mm. mercury, even if it takes a liter or more to do so. This cannot be made a routine procedure and must be kept under the immediate supervision of the physician, for the injection should be interrupted at the first sign of respiratory discomfort, or the development or increase of pulmonary râles. If you set up the infusion and then go off for a time with the expectation that all will go well, you stand a good chance of finding the patient in pulmonary edema when you return. There is no fixed dose of plasma. The proper dose is that which will fill the vessels sufficiently to raise the blood pressure to a safer level, usually around 100 mm. systolic, without inducing pulmonary edema, and the amount that will

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keep it there or higher. I am also inclined to suspect that the intravenous infusion of glucose in water or saline in these cases may do more harm than good, for it seems that the fluid passes so quickly into the pulmonary tissues giving rise to edema of the lungs.

DR. CHARLES H. WHEELER: Why do you think these patients go into shock, Dr. Eggleston?

DR. EGGLESTON: The interference with cardiac function gives rise to circulatory changes which result in secondary peripheral vascular failure.

DR. WHEELER: I have always thought of it as largely due to the fact that the cardiac output is substantially reduced. However, I have never been able to understand how administering fluids can help in a person whose heart already cannot do the work that is required of it. What do you hope to gain by treating the shock?

DR. EGGLESTON: The heart output may be improved by supplying more fluid. I believe that the peripheral circulatory collapse is to a considerable extent secondary to loss of fluid caused by the profuse sweating and the nausea and vomiting that occur in these patients.

DR. GOLD: Perhaps a word at this point, about one way in which the mechanism is formulated, may help to tie things together. In coronary thrombosis, it is a fact that the cardiac output falls, the circulation slows down and in one type of reaction the heart is unable to deliver as much blood as it receives. They develop the syndrome of congestive failure. Under such circumstances infusions are likely to make matters worse. In another type of reaction, there are the same initial phenomena, namely, sudden fall in cardiac output and slowing of the circulation. Events then take a different course. The slowing of the circulation may be so pronounced that sufficient anoxia develops to increase seriously the permeability of the capillaries. Fluid passes into

the tissue spaces, the blood volume falls and hemoconcentration results. Now the heart fails to receive as much blood as it can deliver even in its weakened state. It starts out as acute forward failure of the heart, but capillary paralysis takes over with a train of self-propagating circulatory changes which soon become irreversible and lead to disaster. The administration of plasma increases the volume of blood and volume of circulation.

DR. WHEELER: May I say something else, Dr. Gold?

DR. GOLD: Yes.

DR. WHEELER: No one has mentioned two factors that are, I think, most important in the treatment of angina. I am sure that most people agree on the importance of convincing the patient with angina that he is not going to drop dead. The term angina has a bad reputation among the laity and much good can be done by reassurance. The second point is to teach them the importance of doing things slowly. It is all very well to tell them to take it easy, to avoid hard work or to refrain from doing this or that. But I think a great deal of this advice misses the mark unless the importance of the speed at which they do things is duly impressed upon them. I think it is a fact that a great many people with angina can do almost anything they wish to, if they do it slowly enough, although they may not be able to walk one block without pain if they do it at a rapid pace.

DR. EGGLESTON: I agree. I tried to include that in the very broad general statements that I made in the beginning, regarding the re-education of the patient, the careful study of the patient and of the factors which precipitate his angina and to eliminate those.

DR. STEWART: There is one more drug that was not mentioned, namely, theobromine and sodium acetate. In Riseman's very well controlled study of the drugs which are useful in taking care of patients

with angina pectoris, it rates high and I think next to nitroglycerin in preventing expected angina after a controlled amount of exercise.

DR. GOLD: How does it rate in your experience, Dr. Pardee?

DR. PARDEE: Very satisfactorily. I personally feel a little more enthusiastic about the theophylline-theobromine type of drugs than Dr. Eggleston indicated. I do not think that the number of patients who show striking changes with these drugs is large, but there are some who certainly do show symptomatic improvement. I, therefore, believe it does something to the heart which is beneficial, which may not in all cases be sufficient to put the symptoms below the threshold of sensation, but which in all cases must have some action.

DR. GOLD: Are you sure it is not simply a placebo?

DR. PARDEE: I do not think it is entirely due to a placebo type of action because of the way patients react. I know that experiments have been performed in which placebos have been given, and it has been concluded by excellent observers that placebos are just as beneficial as the supposedly active drugs. But I have seen things happen which made me think that the drugs are really active. I think that both aminophylline and theobromine and sodium acetate are effective. One cannot decide which is better without a long series of experiments.

DR. STEWART: There is a good paper in a recent issue of the American Heart Journal, by Mokotoff and Katz, which I think gives controlled data relating to this. They show statistically in large series of animals that aminophylline given in amounts comparable to those used in the clinic reduced the size of cardiac infarction in dogs.

DR. GOLD: I agree it is a fine study, and there is indication in it that aminophylline and papaverine may reduce the size of an experimental infarct in the dog. But it is not quite safe to infer from it that such

effects are likely to occur in man after the usual oral doses. Mokotoff and Katz gave 15 mg. of aminophylline per Kg. intravenously as the first dose, the equivalent of an intravenous dose of about 1 Gm. for a man, then the same dose twice a day subcutaneously for seven days, then once a day subcutaneously for forty-nine days. These are quite outside the range of doses that are given to humans.

Dr. Travell, have you anything to say about experimental infarction?

DR. JANET TRAVELL: Several years ago we made a study in cats similar to the one you cited in dogs. The size of the infarcts were measured by the blind test by Dr. Gold. In the cat, aminophylline failed to influence the size of the infarct.

DR. GOLD: I should add at this point that in a study we made of 100 patients with the angina of effort in our clinics, only one could distinguish theobromine or aminophylline from sugar of milk or other placebos when both the patient and doctor were kept in the dark at the time regarding the medication. The exception was a man who we learned could distinguish a difference in taste. Before we were able to eliminate that source of error he died of a coronary occlusion, and with that there vanished the possibility of proof in what might have been our single positive case in 100 patients with cardiac pain.

STUDENT: Dr. Gold, I should like to know what is the danger of giving digitalis to one who has suffered a myocardial infarction.

DR. EGGLESTON: There is the fear of rupture of the softened area of the heart or of producing one of the serious arrhythmias, although I personally have never been convinced that I have seen either accident as a result of its use.

INTERNE: Are there reports of occurrences of such accidents? If there are none, I should think that the patient who is going into shock as a result of a myocardial infarction might well be digitalized rapidly.

DR. EGGLESTON: Digitalis would not in any case be used against secondary shock. It might be of value in the primary circulatory depression by improving the contraction of the damaged heart if the possible danger of throwing the heart with its damaged area of muscle into an uncontrollable and possibly fatal disturbance of rhythm, ventricular fibrillation, can be disregarded.

Does that answer your question?

INTERNE: Not quite. You said you never saw it. Have you heard of it?

DR. EGGLESTON: Yes, I have. I might add that it is not usually possible to prove the occurrence of ventricular fibrillation because the termination of life occurs so shortly thereafter that we seldom have an opportunity to establish it definitely by electrocardiographic records.

DR. McKEEN CATTELL: But ventricular fibrillation is a frequent cause of death in occlusion, is it not?

DR. EGGLESTON: Yes, and probably more so in cases of digitalis poisoning with occlusion.

DR. GOLD: Dr. Stewart, do you fear digitalis in patients with heart failure and coronary thrombosis?

DR. STEWART: Early if you have heart failure in coronary thrombosis you have to use digitalis and I do not think you have much worry about it; late also you do not have much worry about its use. It is certainly somewhere around the seventh or tenth day when necrosis is most marked that there is a real danger of rupture. There has been one instance of rupture here which I believe was due to such a cause. If one watches a patient before and after rapid digitalization, it is possible to distinguish differences in the cardiac contraction. After the drug has been given the beat is forceful, the thrust becomes more marked.

DR. CATTELL: Do you believe that the actual pressure against the infarct is greater after digitalis?

DR. STEWART: I think the force of contraction is much greater and if you have a certain amount of blood in that cavity to force out and you have a weak spot, you might have a blowout.

DR. CATTELL: That would depend on the production of a higher pressure, would it not? You have to assume that the pressure was raised. I am not sure there is proof of that.

DR. EGGLESTON: I do not think I have ever seen a blowout of the ventricle that I thought was due to digitalis.

DR. GOLD: How about you, Dr. Pardee? Did you ever withhold digitalis in a patient with heart failure because a myocardial infarction was there?

DR. PARDEE: I do not give it to patients in shock, but to those with signs of heart failure, I use it in less than the usual doses, because of the experimental work which shows that the heart with infarction is more liable to ventricular fibrillation from digitalis. I use about half of the ordinary dose in such cases.

DR. TRAVELL: Some years ago a study was published from this laboratory which showed that cats take 25 per cent less than the usual fatal dose of digitalis to produce ventricular fibrillation after experimental infarction.

DR. GOLD: I have often wondered about the practical significance of that fact since the safety margin is so large in clinical digitalization.

DR. EGGLESTON: I do not usually use the full digitalizing dose at once in the presence of myocardial infarction.

DR. PARDEE: Granting that there is a safety margin, one might still exceed the limits of safety with the usual dose, if the patient happens to be 25 per cent more susceptible than the average and then has an additional 25 per cent increased susceptibility brought on by the coronary thrombosis. We must be wary because ventricular fibrillation may be fatal.

DR. GOLD: I agree it is a good plan to keep digitalization on the light side in these cases, but it will keep us from exaggerating the danger of digitalis if we remember that nearly double the average digitalizing dose is without serious consequence in the average case of heart failure.

I should like to remind you that the risk of digitalis in myocardial infarction has been considered here only in relation to the danger of cardiac rupture and ventricular fibrillation. Two other possible dangers have recently been pointed out. There are some observations that digitalis shortens the coagulation time of blood. It is denied by others. In the *J. A. M. A.* of August 4, 1945, there is a report by Askey and Neurath in which they fail to find increased blood clotting as a source of trouble, but point to the danger of death from emboli in the systemic circulation dislodged by the increased contraction of the heart. I am not impressed with the evidence for either of these dangers. The paper by Askey and Neurath deals with a group of terminal cases. It clearly shows that old age, long-lasting fibrillation and congestive failure bring about a state in which a high incidence of fatal systemic emboli is encountered, but the groups are not sufficiently large or comparable to establish the rôle of digitalis in dislodging these emboli.

It looks like our time is up. There still remain a number of important issues regarding the treatment of coronary disease which we have not touched. I think it would be well to resume the subject at this point in next week's conference.

SUMMARY

DR. GOLD: Let me now briefly sum up the essential points that were discussed today. It was pointed out that there are several clinical varieties of coronary artery disease, each requiring special attention in treatment. Dr. Eggleston presented a brief outline of the essential aspects of the therapy

of this disease. Special attention was paid to the matter of the treatment of shock in acute coronary thrombosis with the use of clyses, glucose infusions and plasma. The view was expressed that attempts at the specific treatment of shock may do more harm than good, while others maintained that infusions, especially of plasma, are in some of these cases a life-saving measure. The rationale was discussed and the dangers were pointed out. Patients with coronary artery disease are often in the state of fear and apprehension arising from the reputation of this disease as a cause of sudden death, and it was urged that all measures possible be taken to reassure them and to point out that they are able to do a great many things if they will only curtail the speed of activities to the limits of their capacity without distress. The eternal question of the purines was explored. There are those who believe that theobromine and sodium acetate is very valuable in the control of the angina of effort, those who believe its action is that of a placebo, and there are the various shades of opinion between these two extremes. The significance of the observation that aminophylline reduces the size of the experimental infarct in dogs was questioned on the grounds that it is apparently not applicable to all species of animals since it does not occur in cats, and on the grounds that the dosage which was used in dogs was so large as to be out of line with the dosage commonly used in man. There was the question of the use of digitalis for the treatment of heart failure which sometimes occurs in patients with coronary thrombosis. The discussion covered the various supposed sources of dangers, ventricular tachycardia, rupture of the heart, increased blood clotting and dislodgment of emboli to the systemic circulation. Not all people are equally impressed with the evidence for any of these dangers when digitalis is employed in proper dosage.

(To be continued.)

Case Reports

Isolation of Virulent *Treponema pallidum* from Human Aorta Thirty-two Hours after Death from Cardiovascular Syphilis*

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AFTER a comprehensive review of the literature on syphilitic aortitis, Longcope¹ stated in 1913: "... the presence of spirochetes in these lesions, as might be expected, cannot by any means be constantly demonstrated with Levaditi stain. . . That these organisms are *Treponema pallidum* seems almost certain though actual proof of such by culture from the arterial lesions, a most difficult task, or direct inoculation into animals, has not as yet been accomplished."

The above statements hold true today. The demonstration of spirochetes in tissue sections, in spite of recent improvements in staining method, is still a difficult task, while cultivation on artificial media has not been successful. Search of the literature failed to reveal any report on the demonstration of *Treponema pallidum* by direct inoculation into animals of aortic tissue obtained from human cases.

We believe that the demonstration of the causal relationship between *Treponema pallidum* and the aortic lesion must in the end rest upon the isolation of viable organisms by animal inoculation.

Recently, a patient in the Peiping Union Medical College Hospital died of cardiovascular syphilis and presented gross changes in the aorta at autopsy. The material ob-

tained from this source was considered suitable for inoculation into rabbits. As the result, virulent *Treponema pallidum* was isolated from the aortic tissues. This single observation seems worth recording as it is the first time, according to our knowledge, that living treponemes have been shown to be present in the walls of the diseased aorta. Furthermore, the isolation of virulent *Treponema pallidum* from cadavers, many hours after death of the patient, is of practical importance to the pathologist, from the standpoint of possible infection at the autopsy table even though the infection with syphilis has been of long standing.

CASE REPORT

H. Y. C. (No. H-74404), a Chinese rickshaw puller, forty-six years of age, was admitted to the out-patient clinic on October 21, 1940. His main complaints were pulsations in the abdomen and neck and nocturnal dyspnea. The illness began in February, 1940. Since March, he experienced also a burning and distending pain beneath the upper end of the sternum, together with epigastric pain which was not related to meals.

The dyspnea was paroxysmal in character and the patient had usually two or three attacks each night. In order to relieve the suffocating sensation he had to sit up or walk about. He was usually free from symptoms in the day time.

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From May to August, after taking some Chinese drugs and bed rest, he was practically free from symptoms. He then became a peddler. However, the symptoms returned in September with increased intensity; he became orthopneic and his sleep was disturbed.

Following repeated venereal exposures a genital sore appeared when the patient was twenty-two years of age. For this sore he took several doses of Chinese medicine by mouth in addition to the local medication. He never received injections. Several asymptomatic subcutaneous nodules appeared at both greater trochanteric regions over twenty years ago. Subsequently, he enjoyed good general health up to the time of his present illness.

Examination showed a sick and distressed individual with marked pulsations in the neck. The findings of interest were limited chiefly to the cardiovascular system. The heart was moderately enlarged to the left and the retro-manubrial dullness was widened. A systolic thrill was detected over the apex of the heart. There was a loud systolic as well as a diastolic murmur at the base, which was louder in the aortic than in the pulmonic region. At the apex of the heart, a loud systolic murmur and a rumbling diastolic murmur were also audible. Pistol shot sounds, Corrigan's pulse and capillary pulsations were present. The blood pressure was 130/42 mm. of mercury.

Moist râles were heard in the lung bases. The liver and spleen were not palpable. The tendon reflexes of the lower extremities were absent except for the right knee jerk which was elicited with difficulty. The pupils and ocular fundi were normal. Matted subcutaneous, hard, non-tender, large nodules, measuring 2 to 5 cm. in diameter, were found over both greater trochanteric and at the sacrococcygeal regions.

The blood serum gave strongly positive reactions to the Wassermann and Kahn tests, but the spinal fluid was entirely normal. Roentgenologic examination showed that the heart was 50 per cent over size and not boot-shaped. The enlargement was chiefly to the left. The pulmonary conus was prominent. The aorta was prominent with suggestive calcification along the ascending and descending portions but without definite dilatation. The subcutaneous

nodules were seen as homogeneous soft tissue masses over the greater trochanteric region. The electrocardiogram showed a flat T in lead 1, depressed S-T in leads 2 and 3, slurred R₃, and R₄ averaged about 2 mm. in height—findings suggesting myocardial damage and coronary insufficiency. There was no axis deviation. The circulation time was 19 seconds by the saccharine method. The blood picture was one of mild anemia. The urine was normal and the phenolsulfonphthalein excretion was 55 per cent at the end of two hours.

The above history and findings led to the diagnoses of cardiovascular syphilis with aortic insufficiency, narrowing of coronary ostia, cardiac enlargement and failure, syphilitic juxta-articular nodules, and questionable syphilis of the central nervous system.

Digitalization resulted in some improvement in the cardiac condition, though slowly. The patient was admitted to the ward on November 13th where there was considerable improvement in his condition following bed rest and the administration of digitalis, potassium iodide and hypertonic glucose solution. After a month's stay he was discharged from the hospital with instructions to have further rest and to continue digitalis. Perhaps because he failed to carry out the instructions, his condition became worse.

When again admitted to the ward on February 15, 1941, the patient was found to be very sick, with orthopnea, marked pulsations in the neck, cold sweats and Cheyne-Stokes respiration. In addition to the findings noted on the previous admission, the liver was 5 to 7 cm. below the costal margin, and the genitalia and the lower extremities were slightly swollen. He died eighteen hours later.

Autopsy Findings. The corpse had been kept in the ice-chest for twenty-eight hours before the autopsy (No. A3426) was performed. The findings of interest were limited chiefly to the cardiovascular system and the subcutaneous tissue.

The heart (Fig. 1) weighed 740 Gm. and was hypertrophied and dilated. The hypertrophy was particularly noticable in the left ventricle. There was diffuse thickening of the aortic cusps. The anterior and posterior right cusps were



FIG. 1. Note the hypertrophied wall and dilated chamber of the left ventricle, the thickened aortic cusps, the gaping of the aortic commissure (A), and the fusion of the anterior and posterior right cusps. The aorta shows both syphilitic and arteriosclerotic patches.

fused together while the two posterior cusps gaped a little at their angles. The free margin of each cusp was thickened, round and rigid.

A longitudinal cut of the rigid margin of the aortic cusp revealed a central yellowish area surrounded by a zone of whitish glistening fibrous tissue. Microscopical examination showed that the yellowish area was composed of necrotic tissue, containing degenerated leucocytes and plasma cells. (Fig. 2.) No spirochetes could be demonstrated in the sections.

The mitral valve showed moderate diffuse thickening with two whitish patches on the anterior cusp but there was no vegetation. The tricuspid and pulmonary valves appeared to be normal.

The orifice of the right coronary artery was completely occluded while that of the left was narrowed. The coronary arteries showed very slight atheromatous change.

The aorta was moderately dilated in its entire length. Its intima presented multiple, large and small, elevated, hyalinized, grayish and yellow patches over the entire length of the aorta (Fig. 1), but especially numerous in the ascend-



FIG. 2. Low power view of aortic valve. Note marked fibrosis, lymphocytic infiltration and necrosis. $\times 44$.

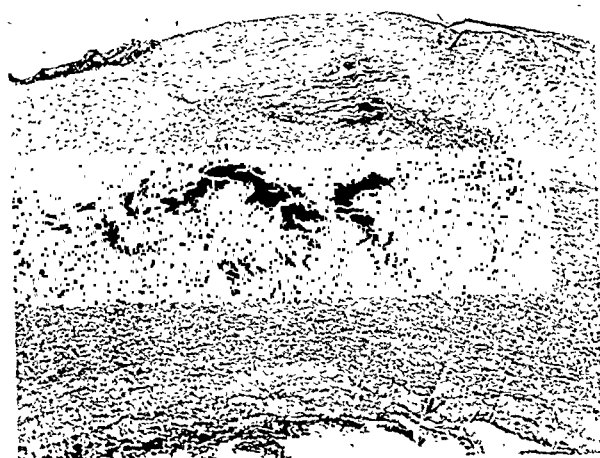


FIG. 3. Low power view of aortic wall. Note extensive scarring and necrosis (dark areas) of intima and media with perivascular lymphocytic infiltration in media and adventitia. $\times 35$.

ing arch and in the lower abdominal portion. Some of these patches showed ulceration or calcification. In between these patches, longitudinal shallow and deep furrows, characteristic of syphilitic infection, were observed.

Under the microscope, the intima was found to be much thickened with marked fibrous tissue proliferation. The media contained numerous irregular scars, foci of lymphocytic infiltration, and areas of necrosis which sometimes extended into the intima. (Fig. 3.) Spirochetes were not found in the sections stained by the Levaditi method.

On gross inspection, the subcutaneous nodules were grayish, firm and without definite capsule; the cut surface was glistening and whitish. Microscopically, they consisted of dense, hyalinized, fibrous tissue together with multiple foci of lymphocytic infiltration. The capillaries were congested and there was

vascular lymphocytic and plasma cell infiltration. No spirochetes were found in the sections stained by the Levaditi method.

ANIMAL INOCULATION

Aorta and Aortic Valve. A piece of tissue measuring 3.5 by 1.0 cm. was removed from the anterior aortic cusp and the adjacent aortic wall. (X, Fig. 1.) For the purpose of sterilization of the surface tissue, the specimen was immersed in 80 per cent ethyl alcohol for three minutes followed by thorough washing (five times) in sterile physiological saline. Then the material was cut into small pieces and ground in physiological saline. Two cc. of this emulsion was injected into the right testis while the remainder (0.5 cc.) was injected into the left scrotal sac of the same rabbit* on February 17, 1941.

Fifty-three days after the inoculation the right testis was somewhat full and felt indurated. The induration increased during the subsequent week. A moderate orchitis had developed by the next week. The material aseptically aspirated from this testis contained actively motile *Treponemata pallida*, as seen under the darkfield microscope. The left scrotal sac never showed any change.

Mitral Valve. A piece of tissue measuring 1.5 by 1.0 cm. was obtained from the mitral valve, for inoculation into the rabbit, on February 17, 1941. It was sterilized in exactly the same way as was the aortic tissue. The entire saline emulsion (2 cc.) was divided equally and injected into the testes of one rabbit. In the subsequent eighty-eight days, no change could be detected in the testicles. The testicles and popliteal lymph nodes of this animal were transferred into a second series of two rabbits. The latter animals also failed to show any sign of syphilis in an observation period of 111 days.

* The animal was a cryptorchid.

Juxta-articular Node. One of the subcutaneous nodules of the trochanteric region was removed at biopsy. It was finely emulsified in sterile physiological saline, and 1 cc. of the emulsion was injected into each testicle of two rabbits on November 30, 1940. Neither animal showed any clinical evidence of syphilis. On March 27, 1941, both animals were killed and their testicles and popliteal lymph nodes were transferred into the testes of a second series of two rabbits. One of these died of diarrhea two months later without showing any sign of syphilis. The second animal developed a small nodule in the right testis ninety-seven days after inoculation. Under the darkfield microscope, motile *Treponemata pallida* were found in the emulsion of the nodule.

Fresh Blood. One cc. of fresh circulating blood of the patient was injected, immediately after withdrawal, into each testis of two rabbits on November 30, 1940. No evidence of syphilis developed during the following four months. Transfers of the testicles and popliteal lymph nodes into a second series of two rabbits also failed to produce syphilitic infection in an observation period of ninety-seven days.

COMMENTS

It is quite possible that other workers have made attempts to demonstrate *Treponema pallidum* in the aorta by the biological method as reported here. However, we have failed to find any positive result being recorded in the literature. We must attribute the success met with in our case to the combination of a number of favorable circumstances.

First, the patient never received any specific antisyphilitic treatment. Even small amounts of arsenical drugs might have led to a negative result. Cardiovascular syphilis, even in the advanced stage, is usually treated with bismuth and arsenical preparations. But, our patient was critically ill on

admission. When his condition improved to the extent that he could be given anti-syphilitic treatment (as was actually advised) he left the hospital. He died eighteen hours after the second admission to the ward before any specific treatment could be given.

Secondly, the lesions in the aorta as found at autopsy were very extensive and active. The necrosis in the aortic wall (Fig. 3) was remarkable. Such lesions would more likely contain *Treponema pallidum* than the older and less active ones.

Thirdly, the time interval between the death of the patient and the inoculation of the aortic tissue into rabbits was not too long for the recovery of viable *Treponema pallidum*. The tissues were injected into the rabbits thirty-two hours after the death of the patient. The body had been in ice-chest temperature (about 7°C.) for twenty-eight hours and the aortic tissue in room temperature (about 20°C.) for four hours. According to Rosahn,² *Treponema pallidum* in tissues refrigerated for as long as a week should be regarded as infectious.

Taylor,³ Hoffmann⁴ and others have reported accidental innocent infections contracted while performing autopsy. The possibility of infection at the autopsy table should not be overlooked, even though the patient's infection with syphilis has been of long standing. In the present case, virulent *Treponemata pallida* were recovered twenty-five years after syphilitic infection.

The negative result with the inoculation of the blood is of significance. In the absence of any demonstrable spirochetemia, it is reasonable to surmise that the positive results obtained with inoculations of materials from the aorta and from the subcutaneous nodule meant the presence of viable *Treponema pallidum* in these tissues. The syphilitic nature of the so-called juxta-articular nodes has been discussed elsewhere.⁵ The failure to demonstrate *Treponema pallidum*

in the mitral valve is not surprising, since it is well known that the mitral valve is rarely, if ever, attacked by the syphilitic virus. The anatomical changes found in the mitral valve might well have been the result of an old rheumatic infection.

In the case reported here, careful search has been made by more than one individual for *Treponema pallidum* in the Levaditi-stained sections of the aorta, aortic valve, mitral valve, heart muscle and the subcutaneous nodule. But, none could be found. However, by inoculation of the materials into the rabbits, viable *Treponema pallidum* was isolated from the aortic tissue and also from the subcutaneous nodule. Without entering into the debatable question of granular forms of *Treponema pallidum*, both staining and biological methods depend for success, in a large measure, upon the number of *Treponema pallidum* present in the tissue. In our case, the number of *Treponema pallidum* seemed to be too small to allow detection in sections, but it was large enough to insure a positive culture in the testes of rabbits. The superiority of the biological method over the staining method is impressively demonstrated.

Morgan⁶ thinks that the number of the organism of syphilis inoculated into a testis of the rabbit should exceed twenty-five (usually over 100) before a positive result is obtained, and that in general the incubation period varies indirectly with the number of the organisms introduced. According to the latter assumption, it seemed that in our patient the aortic tissue contained more *Treponemata pallida* than did the subcutaneous nodule. The positive result from the subcutaneous nodule required not only longer incubation period but also an extra transfer of tissues to a second series of rabbits.

The venereal history indicated that the patient had contracted syphilis some twenty-five years before his death. The signs of

cardiovascular syphilis lasted about a year. In the intervening twenty-four years the disease was apparently latent.

SUMMARY

Virulent *Treponema pallidum* was isolated from the aortic tissue of a patient who died of syphilitic aortitis with aortic regurgitation. The aortic tissue was transferred into the rabbit thirty-two hours after the death of the patient. Viable *Treponema pallidum* was also isolated from the juxta-articular nodules, but not from the circulating blood nor from the mitral valve tissue. The patient died twenty-five years after acquiring syphi-

lis; without ever receiving specific anti-syphilitic treatment.

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Acute Monocytic Leukemia*

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RECOVERY from a fulminating leukemic state is sufficiently uncommon to warrant reflection upon any instance which suggests such an event. Accordingly, when in the fall of 1941 a patient whom we considered to have acute monocytic leukemia made an unusual recovery we were inclined to report the case. This was deferred by our anticipation that a relapse would ensue and by the war with the departure of one of us to military duty. Now that the patient has remained well for four and a half years we present the following report.

CASE REPORT

This fifty-year old white man entered the Jewish Hospital on November 17, 1941. He had been known to one of us (H. B. W.) for many years through minor illnesses. A periodic examination in December, 1940, revealed no abnormalities, the hemoglobin and erythrocyte counts being normal. The leucocyte count was 3,500, with polymorphonuclears 70 per cent, lymphocytes 26 per cent, monocytes 3 per cent, eosinophils 1 per cent. On July 21, 1941, a mild anemia was noted, erythrocytes 3.8 million, hemoglobin 84 per cent. The white blood cells were 4,350, with polymorphonuclears 60 per cent, lymphocytes 34 per cent, monocytes 3 per cent, eosinophils 3 per cent.

During the first week of November, 1941, he noticed soreness of his mouth and several days later visited his dentist* for local treatment. Because of a temperature elevation and continuing soreness of his gums he was examined on November 15, 1941, when it was noted that his

* Dr. Carlos H. Schott cooperated in the care of this patient.

temperature was 101°F., that there were ulcerating lesions in the buccal mucosa and a small tender lymph node at the angle of the right jaw. The erythrocyte count was 3.6 mil., hemoglobin 84 per cent, leucocyte count 4,900, with polymorphonuclears 22 per cent, the remainder being abnormal.

On November 17th, when admitted to the Jewish Hospital, his complaints were extreme weakness, fever and increasing soreness of the mouth. The skin and mucous membranes were pale. There were ulcerating erythematous lesions in the buccal mucous membranes of both cheeks, more marked on the left where edema of the face existed. The node at the angle of the right jaw was enlarged, otherwise there were no enlarged lymph nodes. The spleen was palpable two finger-breadths below the left costal margin. The liver was not palpable.

On November 18, 1941, the peripheral blood and sternal bone marrow was examined by one of us (H. S. S.) with the following findings: Peripheral Blood: erythrocytes, 2.8 million; hemoglobin, 10.5 Gm.; reticulocytes, 2.5 per cent; platelets, 288,400 (Dameshek's. normal 450,000–850,000); white blood cells, 5900; differential count: monoblasts, 84 per cent; lymphocytes, 16 per cent. The red blood cells were of normal size and shape. No nucleated red blood cells were seen. The platelets appeared fewer than normal. Sternal Bone Marrow: A satisfactory specimen was obtained by aspiration of the body of the sternum. (Figs. 1 and 2.) This was examined with supra-vital and Wright-Giemsa stains. It was apparent that the usual bone marrow elements were replaced uniformly by an abnormal cell. Megakaryocytes were extremely scarce, two being seen on the entire film. Nucleated red cells were very rare, as were granulocytes. An occasional erythroblast and

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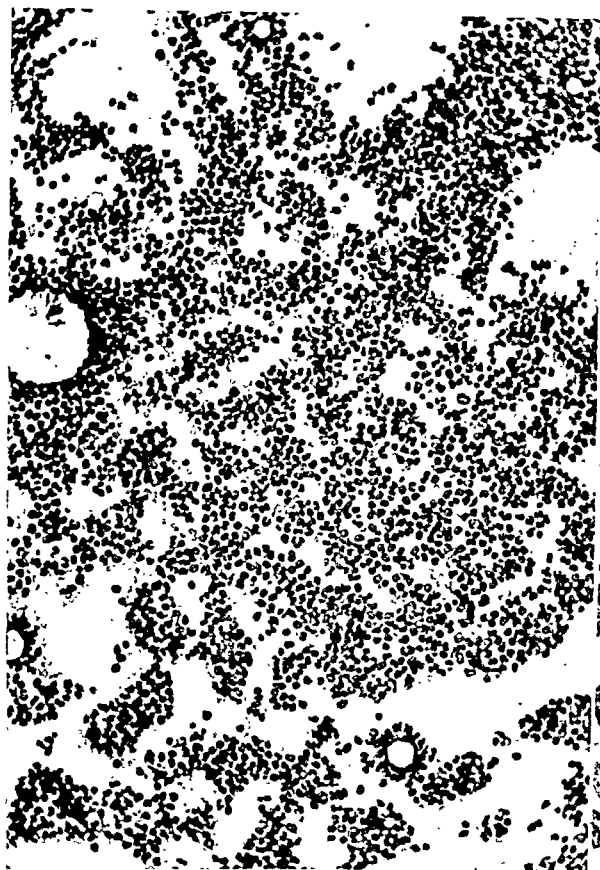


FIG. 1. Sternal bone marrow smear. Low power, magnification 30 \times , demonstrating an infiltration of the marrow uniformly by an abnormal cell. The absence of megakaryocytes is noteworthy.

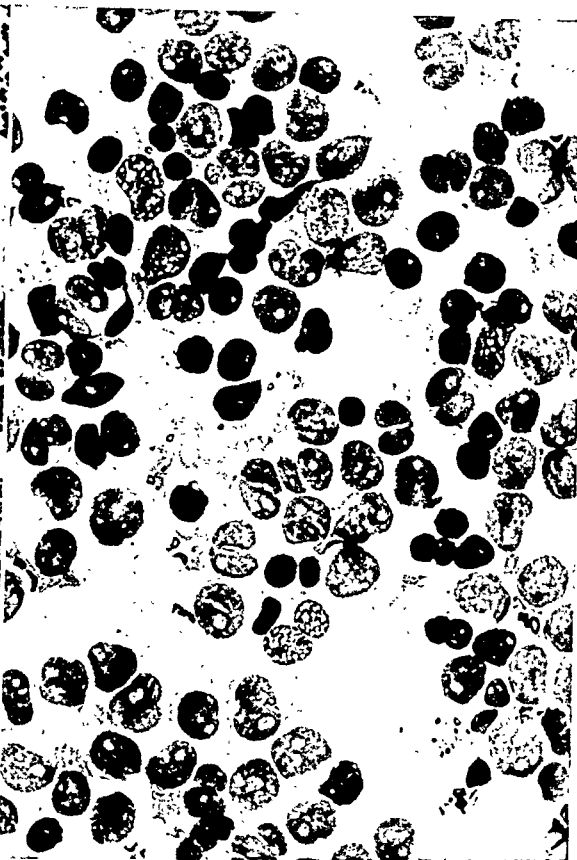


FIG. 2. Same as Figure 1 with magnification 900 \times . The characteristics of the abnormal cells are apparent.

myelocyte were seen. The abnormal cells which made up the substance of the bone marrow appeared "blastic" in type. The nuclei were horse-shoe shaped, indented or double. One to two nucleoli were present. On supra-vital stain many cells had a small collection of neutral red granules in the bend of the horse-shoe, similar to those seen in young monocytes.

This patient was in the hospital 107 days. During the first forty days he was acutely ill. The temperature was a septic type with wide daily swings. (Fig. 3.) He was extremely weak and drowsy. His appetite was very poor and he could swallow only with difficulty. The edema of the face developed into a true noma with spontaneous rupture through the skin. (Fig. 4.) This abscess was opened more fully surgically on December 24, 1941, by Dr. J. Louis Ransahoff. Culture revealed a mixed flora. After this procedure the temperature gradually subsided, the lesion on the face slowly healed (Fig. 5) and his general condition improved. The slow steady progress was temporarily interrupted in the

twelfth week by the development of a left parotitis. This was drained on February 12, 1942, and then treated locally with sulfathiazole packs. A rapid fall in temperature occurred after drainage of the parotitis and the use of sulfadiazine orally, but healing was slow and was followed by a partial left peripheral seventh-cranial nerve paralysis. He was discharged from the hospital on March 3, 1942.

The white blood cells, which on admission were around 5,000, rose on the fourth hospital day to 35,000 and for the next forty days ranged between 25,000 and 40,000. This increase in the white cells was comprised essentially of abnormal monocytes. (Fig. 3.) After the fiftieth day the total white blood cell count was within the normal range and remained so except for a two-week period toward the end of the hospitalization when a secondary leucocytosis developed. This was associated with the appearance of the parotitis described above and the cellular reaction was polymorphonuclear.

Frequent observations have been made during

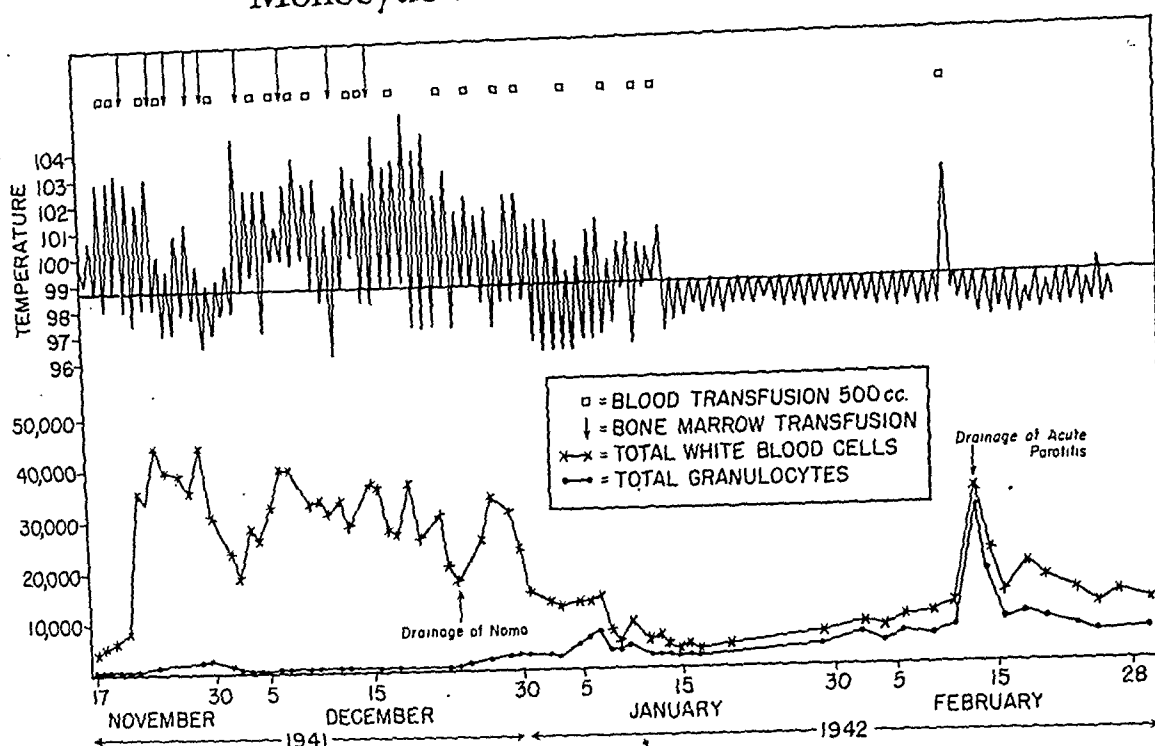


FIG. 3. Graphic representation of temperature, total white blood cells and total granulocytes during hospitalization. The blood and bone marrow transfusions, and the surgical procedures are indicated.

this four-year period, March, 1942, to July, 1946. The patient gradually regained his strength and weight. Residuals of the seventh-nerve palsy persist. A blood count on April 23, 1946, was as follows: Erythrocytes, 5.15 million; hemoglobin, 15.7 Gm.; white blood cells, 5850; polymorphonuclears, 47 per cent; lymphocytes, 44 per cent; monocytes, 7 per cent; eosinophils, 1 per cent; basophils, 1 per cent. The present appearance of his face is seen in Figure 6.

The nursing care in this case can be described only as superb, and is mentioned particularly because we believe it contributed greatly to the recovery. In spite of high fever, anorexia, dysphagia and great discomfort, considerable nourishment was obtained. An adequate fluid balance was maintained by oral and parenteral routes. Twenty blood transfusions were given in the first sixty days. The oral lesions were treated locally by frequent saline irrigations and by gentle removal of dead tissue, by moist heat to the face, and later by surgical drainage through the cheek, followed by sulfathiazole ointment dressings. Sulfathiazole and sulfadiazine were given orally from February 12, 1942, throughout the remainder of the hospital stay. Nine intra-sternal transfusions of sternal bone marrow, each of from 3 to 5 cc., from young healthy donors

were given. The secondary parotitis was treated by incision and drainage, subsequent sulfa-packs and sulfathiazole and sulfadiazine orally.

COMMENT

Whenever one suggests that a patient with acute leukemia has recovered, whether this recovery be defined as a cure or as a remission, he is immediately subjected to the criticism that the patient did not have leukemia. We recognize that this is a natural and sound attitude and we have re-examined our patient in this light.

Clinical conditions which bear more or less resemblance to the case under discussion are infectious mononucleosis, agranulocytosis, leukemoid states and leukemia. Unlike infectious mononucleosis was the presence of anemia without blood loss, absence of lymphadenopathy, and a negative heterophile agglutination. Unlike agranulocytosis may be cited again the anemia, the absence in the history of any of the known agents which produce agranulocytosis and the presence in the peripheral blood and bone marrow of an abnormal cell. The term



FIG. 4. Demonstrating the noma, resulting from spontaneous erosion through the cheek of the lesion in the oral mucous membrane.



FIG. 5. Showing healing of the erosion in Figure 4.

leukemoid has been given to conditions in which large numbers of immature cells, usually of the myeloid series, are found in the peripheral blood associated not with leukemic infiltration of the bone marrow and other internal organs, but with extreme sepsis, with the bone marrow crises of hemolytic anemias, in whooping cough or in metastatic lesions of the bone marrow. Craver¹ states that "in this borderline zone occur the apparent recoveries from leukemia, and it is usual to say that if recovery occurs the disease could not have been leukemia. However, there would seem to be room for speculation as to whether leukemia may not in its early stage be a reversible process and in some cases it is most difficult to decide whether to call the process true leukemia."

The onset of the disease in our case with oral symptoms which sent our patient first to his dentist is characteristic of monocytic leukemia in the experience of Forkner.² The progression of oral infection to the state of noma is seen in leukemia (Kracke³.) The anemia and splenic enlargement are additional features. The platelet count of over 200,000 will be considered not in keeping

with an acute leukemia. By the method used we consider this a definite thrombocytopenia though it still is higher than many instances of acute leukemia. Finally, the diagnosis of leukemia depends upon the demonstration of leukemic cells in the peripheral blood, bone marrow or by infiltration into other organs. The peripheral blood and bone marrow were examined on innumerable occasions and our diagnosis rests upon the bone marrow invasion by abnormal monocytic cells (Figs. 1 and 2) which also were present as indicated in Figure 3 in the peripheral blood. In the first weeks of the disease the clinical and hematologic picture indicated an ominous prognosis and this was concurred in by Dr. Raphael Isaacs who saw this patient with us.

Since the etiology of leukemia is unknown, any explanation for recovery in a given case becomes a matter of speculation. However, there are certain clinical similarities between the natural course of events in acute leukemia, in acute agranulocytosis and in acute aplastic anemia. These similarities are seen in the manifestations of sepsis. It is now generally held that the absence of

granulocytes in acute agranulocytosis permits the rapid development of sepsis and accounts for the fatal outcome in many of these cases. Accordingly we postulate that death in acute leukemia may be due not to the presence of abnormal cells but to the *absence of normal cells*. In acute leukemia the disruption of the bone marrow and subsequently of the peripheral blood may be caused by some agent whose action is less permanent than has been usually assumed. It is conceivable that if the body defenses could be tided over such an insult long enough, normal bone marrow function could be resumed and recovery result.

Accordingly, it is our speculation in this case, that an early diagnosis, unusually efficient nursing care, general supportive measures, many blood transfusions, and chemotherapeutic and surgical attack on the oral infection were effective in maintaining the body defenses until the bone marrow recovered from the insult which produced that cellular reaction we call leukemia. The report of Kugel and Schnitker⁴ of the control of severe granulocytopenia in a case of aleukemic leukemia by the use of penicillin gives support to the concept that the course of this disease may be modified favorably by agents which control sepsis, even though in their case death was the final outcome.

Mention should be made of the use of sternal bone marrow transfusions. Because the prognosis seemed ominous at the outset of our treatment it was thought advisable on the recommendation of Dr. Raphael Isaacs to give transfusions of small amounts of bone marrow aspirated from young healthy donors directly into the sternal marrow of the patient. This procedure had been recommended earlier by Morrison and Samwick.⁵ It was not anticipated that this or any other measure would alter the course of the disease. With the recovery of our patient it becomes necessary to evaluate this procedure. We have tried this method



FIG. 6. The appearance of the face at the present time. The scars of the noma and the secondary parotitis can be seen.

of treatment in four other patients, two with acute monocytic leukemia and two with acute myelogenous leukemia without success. It is only fair to mention that these patients were all seen late in the course of their disease, and perhaps they did not receive as intensive treatment as the present case. One may still speculate that normal human bone marrow contains something which is necessary for the normal development of white blood cells and that this substance is lacking in acute leukemia. Further use of bone marrow transfusions of bone marrow will be necessary to determine its value in the treatment of acute leukemia.

The prognosis in acute leukemia has been so poor that an attitude of hopelessness has naturally developed, as a result of which often no attempt is made along therapeutic lines. With large pools of blood readily available now, and with chemotherapeutic agents, such as sulfa drugs, penicillin and other antibiotics to combat infection, it is to be hoped that more instances of recovery will be noted. The prospects for such recovery depend, at the moment and until more is known about the etiology of the disease, first upon an early and accurate diagnosis, and second, upon an attitude of optimism which is translated into an active and intensive attempt to prevent the complications of the disease, i.e., sepsis and hemorrhage.

CONCLUSIONS

1. A case of acute monocytic leukemia with noma is reported.

2. The patient has been clinically well and the peripheral blood and bone marrow normal for over four years.

3. Treatment consisted of symptomatic care, many blood transfusions, (twenty in sixty days), chemotherapeutic and surgical attack on complicating infections, and nine transfusions of normal sternal bone marrow during the height of the disease.

4. It is suggested that monocytic leukemia may not be as universally fatal as previous experience has indicated.

5. Early diagnosis and intensive treatment directed to prevent the complications of the disease may confirm this statement.

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Editorial

Mechanisms of Edema Formation

REGULATION of the water balance of the body and of the distribution of fluids within the body involves mechanisms which investigations of recent years have disclosed to be more complex than was previously supposed. The results of some of these studies have been summarized recently in two lucid and informative reviews.^{1,2}

Water normally constitutes about 70 per cent of the adult body weight and this proportion ordinarily is maintained with remarkable efficiency by a balance between total water intake and output. Of the average daily total intake of 2,400 Gm. of water, about half is taken as water or other beverage, 900 Gm. as preformed water of food and 300 Gm. is water of oxidation formed in the body during the metabolism of foodstuffs. Of the average daily total output, about 1,300 Gm. of water are excreted in the urine, 200 Gm. in the stools and 900 Gm. are lost through the skin and lungs ("insensible loss"). It will be noted that a large proportion both of the water taken in and excreted is not readily measurable by ordinary methods and is not considered in the common bedside practice of estimating water balance by comparison of urinary output with fluid intake. Sunderman points out the fallaciousness of such comparisons, which so often give discrepant results even if apparently complete twenty-four hour urine specimens have been collected. Daily measurement of the body weight usually gives a more satisfactory approximation of gross positive or negative fluctuations in water balance.

¹ SUNDERMAN, F. W. Approaches to the study of edema and dehydration. *Am. J. Clin. Path.*, 16: 353, 1946.

² ABBOTT, W. E. A review of the present concepts of fluid balance. *Am. J. M. Sc.*, 211: 232, 1946.

The body water may be regarded conveniently as divided into an intracellular component comprising about 45 per cent of the body weight, and extracellular components comprising about 25 per cent of the body weight. Of the extracellular portion, about 80 per cent normally is found in the interstitial fluids and 20 per cent is contained within the walls of the vascular bed. The interstitial and the intravascular fluids are in dynamic equilibrium, with a constant interchange of water, electrolytes and non-electrolytes across the capillary membrane. In edema, the regulation of this equilibrium is disturbed and an excessive amount of fluid accumulates in the intercellular spaces.

Sunderman has divided the various causes of edema into the following categories: (A) primary retention of water (water intoxication); (B) primary retention of salt (as in overadministration of salt, adrenal cortical and gonadal hormones); (C) reduction of colloid osmotic pressure (hypoproteinemia) due to inadequate protein intake, impaired synthesis of serum albumin or excessive loss of proteins through the kidney or other channels; (D) general or local increases in capillary blood pressure (congestive cardiac failure or mechanical obstruction to veins); (E) blockage of lymphatic return of protein-containing tissue fluid.

Investigation of the mechanisms of edema has resolved itself largely into analysis of the factors influencing the exchange of water, electrolytes and non-electrolytes across the capillary wall and of those regulating glomerular filtration and tubular reabsorption of water. The hydrostatic pressure within the capillary bed and the permeability of the capillary membrane are im-

tant factors in the movement of fluid from vascular channels into the interstitial spaces. The colloid osmotic pressure of serum albumin and the tissue tension of subcutaneous elastic tissue are the most significant forces in maintaining fluid within the confines of the capillary bed.

Starling's concept of a simple equilibrium between hydrostatic and colloid osmotic pressures effecting a filtration balance at the capillary wall has been borne out, in general, by clinical investigation and animal experiment. The recent work of Keys and his associates,³ however, has disclosed discrepancies in this relation. In a study of famine edema, which reappeared on a large scale in World War II, Keys placed thirty-four volunteers for six months on a semi-starvation diet of whole cereals, potatoes, turnips, etc., providing an average of 49 Gm. of protein daily. The subjects developed typical famine edema resembling that observed in certain war areas. They lost an average of one-fourth of their body weight and became "waterlogged," with a relative excess of sixteen pounds of extracellular water per man. Like the victims of starvation abroad, the experimental subjects also showed marked polyuria, brady-

³ KEYS, A., TAYLOR, H. L., NICKELSEN, O. and HENSCHEL, A. Famine edema and the mechanism of its formation. *Science*, 103: 669, 1946.

cardia and diminution of heart size, no hepatomegaly and no rise in plasma non-protein nitrogen or chloride. In accord with previous observations, there was no indication that edema was due to renal or cardiac failure, the venous pressure, in fact, being reduced. Thiamine deficiency was ruled out by analyses of food and excreta.

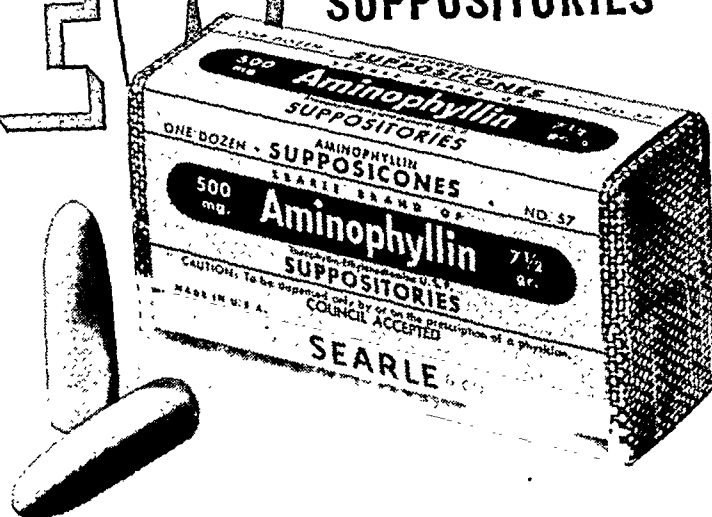
An unexpected result of this study, however, was the finding that, contrary to earlier observations, the development of edema was accompanied by only a slight decline in the concentration of plasma proteins, averaging 0.73 Gm. per 100 cc., and by no marked hypoalbuminemia. The slight degree of hypoproteinemia or lowered colloid osmotic pressure in the plasma observed clearly could not account for the appearance of marked edema. The discrepancy was all the more striking because it was noted consistently in the subjects of this carefully controlled experiment.

Keys interpreted his data to indicate that the fluid balance between blood plasma and interstitial fluid does not reflect a simple equilibrium of the kind generally postulated. He concludes that there is a dynamic nonequilibrium state of the capillary wall and implies transfer activities of the lining endothelium which have yet to be clarified.

A. B. G.

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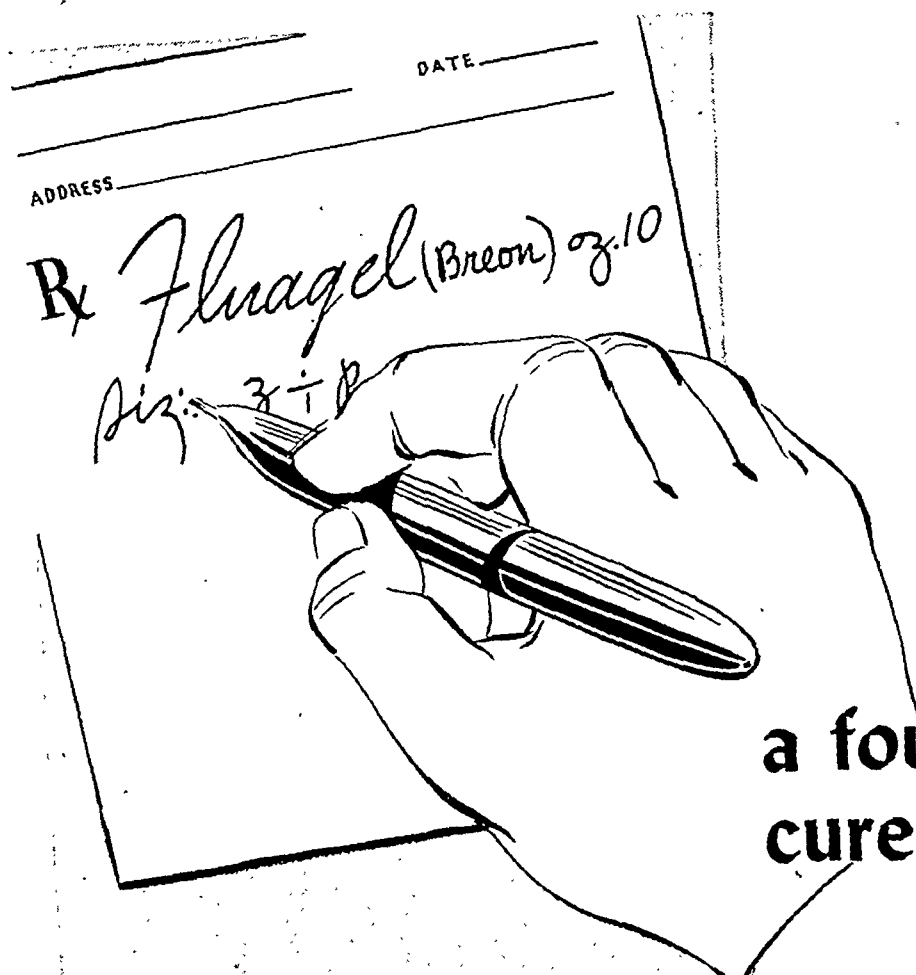
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1. J.A.M.A. 129:1080, Dec. 15, 1945
2. Illinois M. J. 88:85, August, 1945

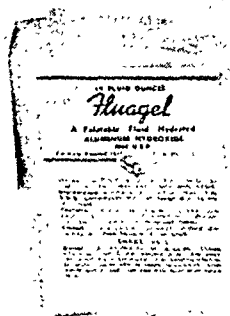
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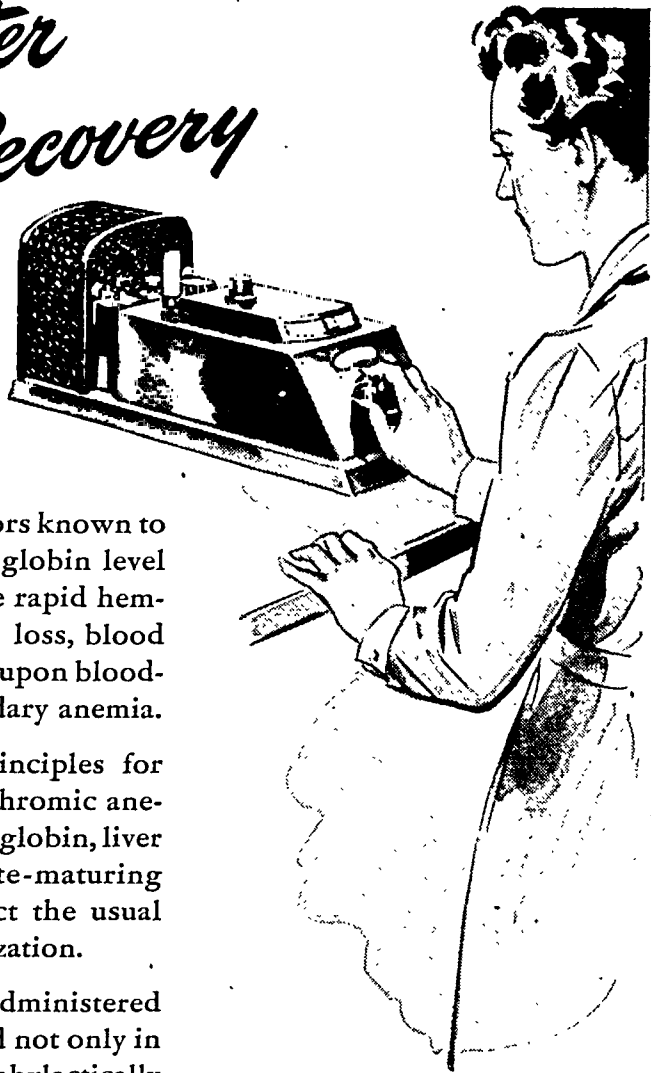
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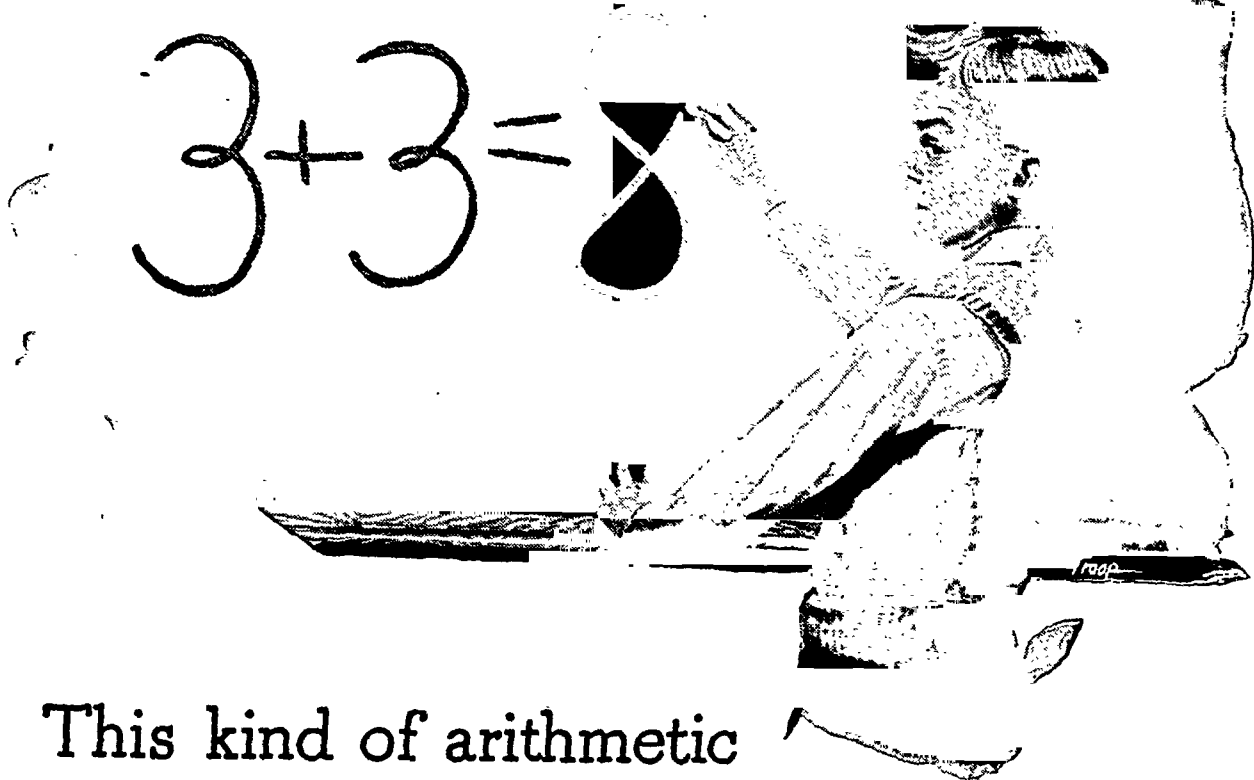


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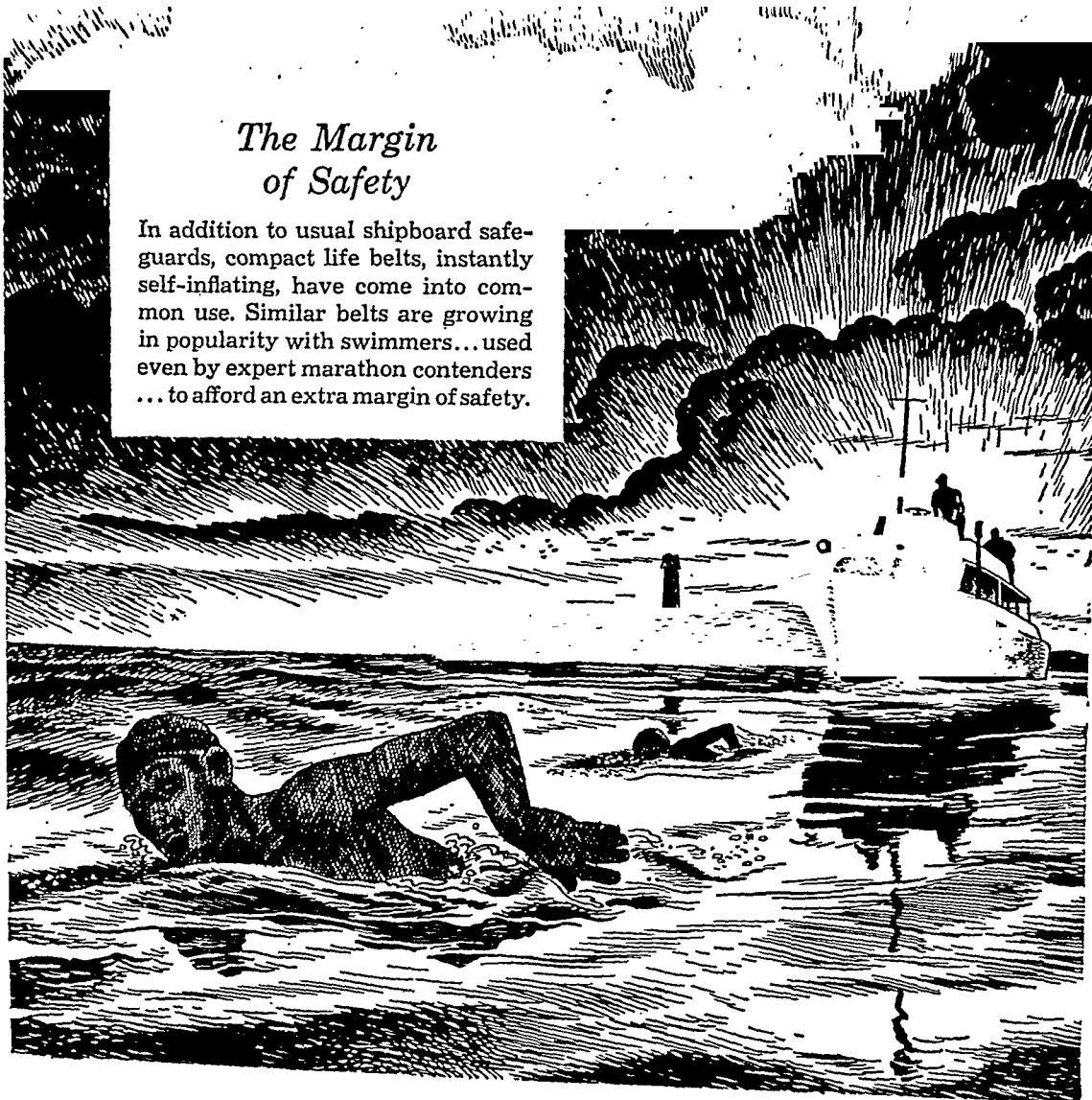
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